THE CHICAGO MEDICAL SCHOOL
QUARTERLY

VOLUME 18, NUMBER 2 MAY, 1957

CONTENTS

THE CHICAGO MEDICAL SCHOOL
QUARTERLY
VOLUME 18 MAY, 1957 NUMBER 2

EVOLUTION AND THE LIVER*

HANS ELIAS, Ph.D.**

The liver is a great big, brown organ which appears quite uninteresting. It lacks the dynamic appeal of the heart or the brain and is so sturdy that it rarely causes noticeable trouble. Yet, its morphology yields unexpected insight into some aspects of evolution.

Morphology is not the mere description of structures and shapes, but it is a large field, the chief aspects of which are historical. Morphology of an organ begins with its earliest appearance among primitive animals and ends with its degeneration in disease, just as the history of a star begins with its hypothetical condensation from a hydrogen cloud and may end with its explosion as a supernova and final contraction.

The studies to be reported here began in 1947 by the accidental finding of a discrepancy between the classical textbook descriptions of the normal human liver and observed slides. The discovery that the theory of cord structure was untenable and had to be replaced by the theory of plate structure[1,2] was made in the process of preparing illustrative material for teaching.

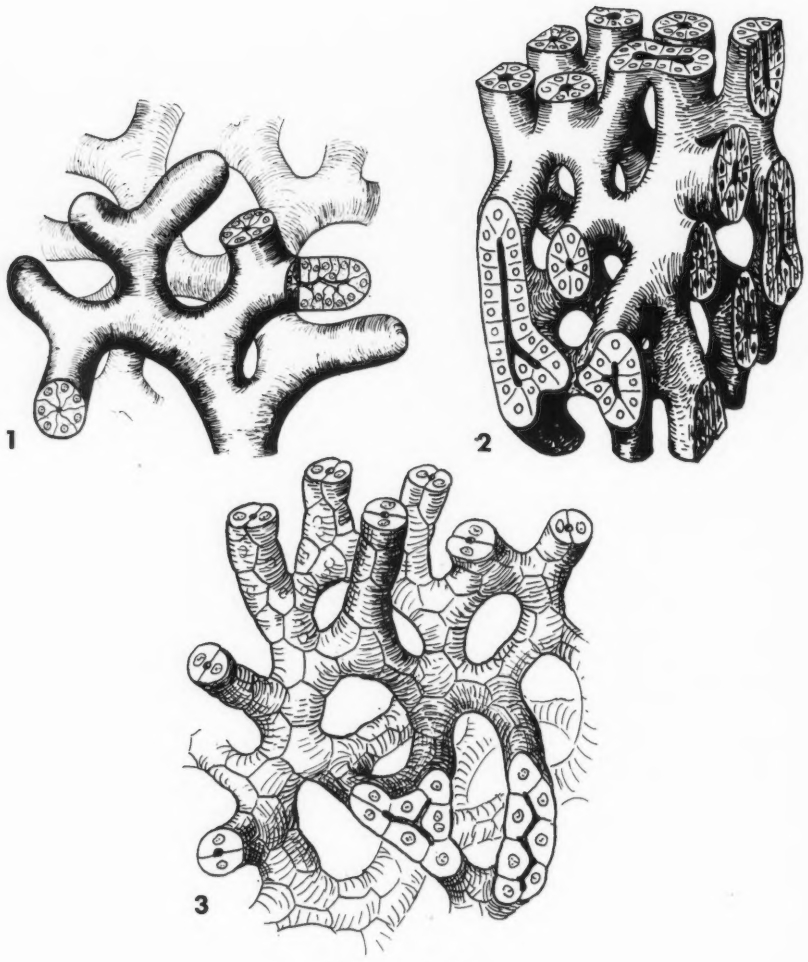
From then on, further studies were guided chiefly by the writer's interest in evolution. These studies led into the fields of comparative micro-anatomy, comparative embryology, pathology and oncology. This long road of investigations was strewn with unexpected findings, many contradicting, some supporting established biological principles.

Allegedly there had been a gradual evolution of the liver from the cyclostomes to man, beginning in the former with the structure of a ramified tubular gland (Fig. 1). The blindly ending tubules had become connected into a network, so that the livers of fishes, amphibians, reptiles and birds were "net-like tubular glands" (Fig. 2). Finally, in the mammals, it was reported, the tubules had become narrow, two cell thick cords united in a net (Fig. 3).

In 1947, these viewpoints were "firmly established". However, nothing of all of it was correct. We have described in another place[3] the psychological failings of two generations of anatomists, which erected this fictitious picture of liver evolution. These men were dominated by blind confidence in the published opinions of their predecessors. Their own observations—and they were excellent observations—were distorted to fit the established theory. No original observations would be needed; but the mere study of the illustrations of these nineteenth and twentieth century authors, assuming that the illustrations presented typical or average fields of vision would suffice to show the inaccuracy of the opinions at which these same authors arrived. Throughout the literature on liver morphology from 1849 to 1947 this discrepancy between observation and in-

*Partially aided by grants from the U.S. Public Health Service and the American Cancer Society.

**Associate Professor of Anatomy, The Chicago Medical School.



Figures 1 to 3

Figures 1-3. **Stereographic presentations of supposed structures of vertebrate livers, subsequently shown to be incorrect: 1. hagfish; 2. most lower vertebrates and birds; 3. mammals.**

terpretation dominates the picture. There was but one exception: The distinguished anatomist Bluntschli, at that time (1904), a young beginner, dared to say that his observations did not bear out exactly the existing doctrines. But he admitted that either his specimens must have been poorly preserved or that he, because of his lack of experience, was incapable of understanding how his slides could be reconciled with the logical theory.

Our studies[1, 3, 4] of the livers of 42 species taken from every class and many orders of vertebrates were carried out by three methods of three-dimensional investigation: 1) examination of very thick slices under varying focus; 2) wax plate and glass plate reconstructions from serial sections; 3) the statistico-geometrical method as developed by the writer and several co-workers.[5]

The livers of all vertebrate animals

have the same basic structure.[a] The adult vertebrate liver is a system of connected walls, called a *muralium*. As the walls in a large building, an art gallery for example, enclose rooms between them, so the liver plates or walls, *laminae hepatis* enclose *lacunae*. As the walls in an art gallery have doors through which neighboring rooms communicate, so do the *laminae hepatis* have holes in them through which neighboring *lacunae* anastomose. Thus a vast network of spaces, the *labyrinthus hepatis* is formed, comparable to the vast maze of rooms and corridors in the gallery (Fig. 4). And as the walls of many museums are lined with burlap so that a narrow space exists between the masonry and the fabric lining, so is the *muralium* of the liver lined with a specialized endothelium. Between it and the *laminae hepatis* exists the narrow tissue space of Disse.

Now this endothelium encloses a vast, three-dimensional network of *sinusoids* through which blood flows.

The liver of all vertebrates[b], thus, is a *muralium* inserted in the blood stream from the intestine to the heart.

This is so in the most primitive vertebrate, the hagfish and in the most advanced, the songbirds and man. From the most primitive to the highest of the vertebrates, practically no evolutionary change has occurred in the liver. In fact, *the adult liver is the most uniform organ of the vertebrates.* And since no liver-like organs are known to exist in invertebrates (including even Amphioxus), the vertebrates could also be called *"Hepatata."*

There exists but one, though minor, structural difference among livers: The liver of the lower vertebrates has two-cells thick plates (it is a *muralium duplex*) while the liver of songbirds and that of mammals has one-cell-thick plates (it is a *muralium simplex*), (Fig. 4). The liver of amphibians is intermediate in structure, i.e. its plates vary between one and two cells thickness. And among the

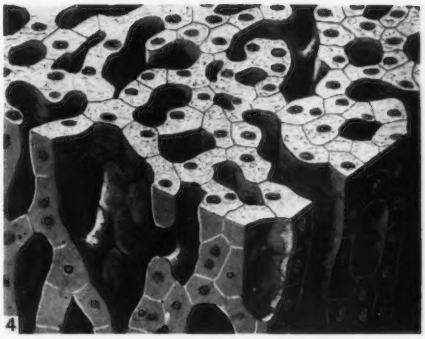


Figure 4. **Reconstruction from serial sections of a small portion of a human liver.**

lower birds we find *muralia duplica* and *muralia simplica*, sometimes both types within one genus. The *muralium simplex* appears to be of better mechanical construction and greater physiological efficiency than the *muralium duplex*, as has been explained elsewhere,[6] but this difference is of little significance when compared to the overall uniformity of this organ throughout the vertebrates.

One would expect, then, that an organ so constant in its adult structure would show a great uniformity of embryonal development. This also is a point on which all embryologists agreed. It was the consensus of opinion that the liver of all vertebrates arose from a tubular and branching evagination of the intestinal wall. Again, dogmatism and a firm belief in von Baer's "laws" of embryogenesis and in the biogenetic "law" of Muller and Haeckel and in the doctrine of specificity of germ layers blinded many investigators against the evidence of their own observations. The literature and psychology of this phase of liver morphology has been critically reviewed at another occasion.[7]

Just as all my distinguished teachers, and as such I consider all the great embryologists of the 19th and early 20th century, also I was firmly convinced that the liver of all vertebrates arose as an evagination of the gut wall and was purely entodermal.

How great was my astonishment when I saw mesenchyme cells change into liver

(a) With the exception of older larvae and adults of the lamprey.

(b) Including even young lamprey larvae.

cells in pig embryos, and when I saw plates of liver cells which arose from a proliferating mesothelium, penetrating between capillaries of the umbilical veins, in the embryos of Madagaskar hedgehogs.

More astonishing than the participation of mesoderm in the formation of liver parenchyma is perhaps the great variety of modes of development which we encounter among various vertebrates. Some vertebrates form their liver from entoderm only, others use a mixture of entoderm and mesoderm. Some do it through cavitation of solid cell masses by blood islands, which later join to form the network of sinusoids. The livers of others are formed of sprouting solid cell cords which penetrate into spaces between preformed capillaries and then fuse into connected plates. Again other livers are formed at first as branching tubular glands; the tubules lay themselves side by side and fuse into two cells thick plates. In one species two hollow entodermal plates lay themselves around the sinus venosus and from them sprout tubules (later to fuse into a *muralium duplex*). These tubules interdigitate with capillaries that sprout from the sinus venosus. In others, trabeculae sprout from a large globular mass of cells, to be hollowed out later by the advancing gut lumen. These fuse still later into a *muralium duplex*. Finally there are vertebrates in which individual cells migrate from a proliferating entodermal diverticulum[8] and from the proliferating mesothelial wall of the coelom, into preexisting intercapillary spaces. These migrating cells unite into connected walls, forming at first a *muralium triplex usque quintuplex*,[c] which later thins out into a *muralium simplex*. This method has been called "interstitial invasion."

Altogether, among 30 species investigated, 12 fundamentally different modes of liver development were found. These are all summarized in Table 1.

But the surprises do not end here. For not only are there at least 12 modes (and probably more will be found as more species are investigated) of "hepatogenesis."[d] There are also two basic modes of "cholangiogenesis"[e] which undergo variations among various forms, for in some vertebrates the duct system of the liver arises by evagination from the gut or by penetration of the gut lumen into the liver primordium, while in others, the terminal ducts form from clusters of liver cells which differentiate into common epithelial cells. In the center of such small cell groups located within the liver, a lumen arises, so that each such group of cells becomes a little vesicle. Gradually all these vesicles join and line up into the system of hepatic ducts. Finally, from their confluence, the common bile duct grows toward the gut until it touches it and finally opens into it.[7, 9, 10, 11] The occurrences of these two kinds of ductal development are listed in Table II.

In other words: twelve different kinds of embryonic liver, together with two kinds of ductal development (i.e. twenty-four modes of total liver development involving one or two kinds of building material, which brings the methods up to forty-eight) produce one identical end result: a *muralium* through which portal blood streams.

I have used[7] the following simile:

The liver has been compared with a building. The liver plates of the *muralium* represent the walls of the house. Let us assume that we intend to build five houses. They shall all be alike. They are to be built according to one common floor plan. No specifications exist, however, as to the material to be used for the walls and as to the method of construction. The five identical houses, therefore can be built in various manners. One of them is being built as a log cabin. In other words, cylinders are brought into apposition, and are cemented together to form walls. This mode of construction is comparable to the tubular development of the liver such as found in selaceans, snakes and birds. A second house is being built in solid masonry, i.e. by cementing individual stones to-

(c) System of walls, 3-5 cells thick.

(d) Development of liver parenchyma.

(e) Development of bile ducts.

Table I

Class	Species (if not original, name of author is in parenthesis)	Entodermal Contribution: quantity	Entodermal Contribution: manner	Mesodermal Contribution: quantity	Mesodermal Contribution: manner
Cyclostomata	Petromyzon planeri	all	Anterior yolk mass forms tubules in situ		
Selachii	Torpedo ocellatum	most	Tubules from 3 secondary diverticula.	little	Irregular cell group from visceral mesothelium.
	Squalus acanthias	most	Primary diverticulum abortive.	some	Tubules from visceral mesothelium
	Scyllium canicula	all			
Teleostei	Salmo	all	Solid mass connected with yolk sac. Internal rearrangement of cells, blood islands.		
	Lebistes reticulatus	?	similar		
Ganoidea	Amia calva	all	Blood islands form in solid cell mass wedged into yolk sac.		
	Lepidosteus osseus	probably similar			
Amphibia	Triturus alpestris (Gianelli) Rana esculenta Rana temporaria (Shore, Weysse) Rana pipiens	all	Anterior part of yolk cell mass is tunneled by blood islands which join to form sinusoids. Yolk cells between them are primitive liver plates.		
Reptilia	Thamnophis radix Thamnophis sirtalis	all	Solid cell mass from which tubules grow. Some blood islands form within cell mass.		
	Alligator mississipiensis	most	Tubules	little	Proliferation from visceral peritoneum, pericardium and parietal pleura
	Chrysemis marginata	little	Solid cell mass tunneled by blood islands, isthmus only.	most	Solid cell mass of visceral peritoneum and parietal pleura tunneled by blood islands
	Lacerta muralis (Brachet) Anguis fragilis (Choronshitzky)	most or all	Interstitial invasion	?	?
Aves	Gallus domesticus	all	One longitudinal, primary diverticulum, 2 secondary, flat, frontal diverticula, tubules		
	Agelaius phoeniceus Passer domesticus	most	Solid mass from which tubules sprout.	some	Proliferation from parietal pleura
	Toxostoma rufum		Tubules	?	
Mammalia	Didelphys virginiana	much	Interstitial invasion	some	Interstitial invasion from visceral peritoneum
	Hemicentetes Setifer spinosus	at least half	Interstitial invasion	perhaps much	Interstitial invasion from parietal peritoneum between capillaries from umbilical vein.
	Lepus cuniculus (Brachet)	much or all	Interstitial invasion	?	?
	Cavia cobaya	all	Interstitial invasion		
	Mus rattus	most	Interstitial invasion	some	Interstitial invasion from visceral peritoneum
	Sus scrofa domesticus	much	First solid trabeculae, later interstitial invasion	much	Mesenchymal transformation
	Microcebus myoxinus Homo sapiens	most	Interstitial invasion	some	Interstitial invasion from visceral peritoneum

Where tubules are formed they join later into two cell thick plates. Where interstitial invasion takes place, the invading cells surround pre-existing capillaries and invest them into walls several cells thick. Where solid cell masses are tunneled by blood islands, these islands join to form networks of vessels which are at once vitelline veins and liver sinusoids.

Table II

Modes of Development of the Duct System

Class	Species	Ducts develop from liver cells or yolk cells and join the gut secondarily	Ducts arise from the gut and advance into the liver
Cyclostomata	Petromyzon planeri	X	
Selachii	Torpedo ocellatum Squalus acanthias Scyllium canicula		X
Teleostei	Lebistes reticulatus	X	
Ganoidea	Amia calva		X
Amphibia	Rana pipiens	X	
Reptilia	Thamnophis radix Thamnophis sirtalis		X
	Alligator mississipiensis		X
Aves	Gallus domesticus Toxostoma rufun.		X
Mammalia	Homo sapiens LEWIS and HORSTMANN	X	

gether. This method is comparable to interstitial invasion. The walls may be constructed of one kind of stone only (purely entodermal livers arising by interstitial invasion: guinea pig). In a third house, the walls may be built in solid masonry (individual stones cemented together, interstitial invasion) but of two different materials, such as of concrete blocks with brick veneer. This method corresponds to interstitial invasion from entoderm and mesoderm (development as found in the primates). The fourth and fifth houses are to be produced in an entirely different way, namely by excavating the rooms in one case out of a solid block of stone, in the other case out of a solid block of clay. The method corresponds to the excavation of solid masses of cells by blood islands which later join to form the network of sinusoids. It is performed with two different materials: entoderm (frog) and mesoderm (turtle).

After the five houses are covered on the outside with stucco and on the inside with wall paper and carpets, no one can recognize, by visual inspection, the different methods and materials of construction.

The most disturbing factor brought forward by these observations is that they contradict the first and second laws of von Baer, namely:

"1. That the common characteristics of a large group of animals are formed earlier in the embryo than the specific, and

2. That from the most general morphological characteristics, the less general ones are formed until, finally, the most specific characteristics appear."

In the case of the liver, the opposite is true: The embryos are diversified, while the adults are alike.

The findings also contradict the Muller-Haeckel law of biogenesis, which postulates that embryos resemble ancestral adults. As far as the liver is concerned, also this is not true, for the livers of young embryos are quite independent of the morphology of their adult ancestors.

It appears that Sewertzoff[12] was quite justified when he said that the question of the relationship between ontogenesis and phylogenesis had been given a somewhat unilateral consideration; for one used to inquire chiefly which influence phylogenesis exerts on the ontogenesis of animals. Sewertzoff then demonstrated that important morphological features of adult fishes and reptiles are the result of variations in their embryos, the embryo developing features which had not existed in the ancestors. He showed that the embryos initiate evolutionary changes of certain characteristics, such as position

and number of rays of fins, body proportions, number of vertebrae, etc. He called the process, "phylembryogenesis." In the cases cited by Sewertzoff a change initiated in the embryo is carried to its full development in the adult.

In the case of the liver, this is not verified. For, as far as the liver is concerned, the embryos initiate very drastic changes. But these changes do not remain permanent. With further development, the histogenesis of all livers leads to a final, common pathway.

It is difficult to understand why, out of this great diversity, a common end result arises. One becomes inclined to see an aim in liver development, to use a finalistic approach. However, as soon as one uses a finalistic or teleological approach, one has lost the solid ground of scientific thought. But, in reality, it is not difficult to find an explanation which does not violate the Darwinian principles.

We agree with Simpson[13] that diversity demonstrates a low but sufficient degree of efficiency of an organ or a process.

Uniformity, on the other hand, indicates an optimal condition, a condition which is not only the best but also the worst possible condition, in other words the only tolerable condition. We can conclude that the structure of a *muralium* pervaded by a network of sinusoids is not only the best, but also the only tolerable structure which a liver can and must have, if the organism is to survive.

Thus while each species begins to build its liver in an arbitrary or capricious or random way, only those species are able to survive who, by chance, have acquired the "habit" of converting their embryonic liver, regardless of its original structure or composition into a vascularized *muralium*.

After having become acquainted with the normal histology of the liver of man and with its history, based on comparative anatomy and embryology, we are ready to take the final step and look at what can become of a liver in disease. We have studied first, a morpoholgically striking disease of the liver, namely cirrhosis.[14] We have learned interesting things from these studies, particularly about the behavior of connective tissue. However, from the standpoint of evolution we were not able to learn anything from cirrhosis, perhaps because it is a strictly degenerative disease.

However, the study of liver cancer, and specifically of primary(f) liver carcinoma, also called hepatocellular carcinoma and hepatoma but better perhaps "hepatocarcinoma," has again shown phenomena which shed much light on the central problem of biology, evolution.

A cell as such is a multi-potential thing. But, normally, since it is located at a specific spot, within a specific organ, it must submit to the discipline of the totalitarian organism. One usually says that if a cell or a group of cells becomes cancerous it "goes wild." That is, that it can grow in any direction and manner it "pleases." Thus, primary liver cancer also appears chaotic at first sight. It can assume many different forms and structures[15] which bear little or no resemblance to a normal liver.

At this laboratory one hundred forty-four cases of human primary liver cancer were studied.[16, 17] Using the above mentioned methods of extrapolation from two-dimensional slices into three-dimensional space, and comparing the observations with knowledge previously gained in comparative histology and embryology, it was possible to classify the various forms of primary liver cancer and to show that cancerous liver cells, though they have freed themselves from the restrictions which the organism had imposed upon them as long as they were its law abiding citizens, nevertheless are bound in their morphogenetic behavior to a firmly established tradition of their vertebrate ancestry.

In Plate I, one sees a summary of the structures which hepatocarcinomata can assume; and on Plate II in correspond-

---

(f) "primary" means that this cancer arises from liver cells, as distinguished from metastatic tumors which have arisen in other organs and have become lodged in the liver.

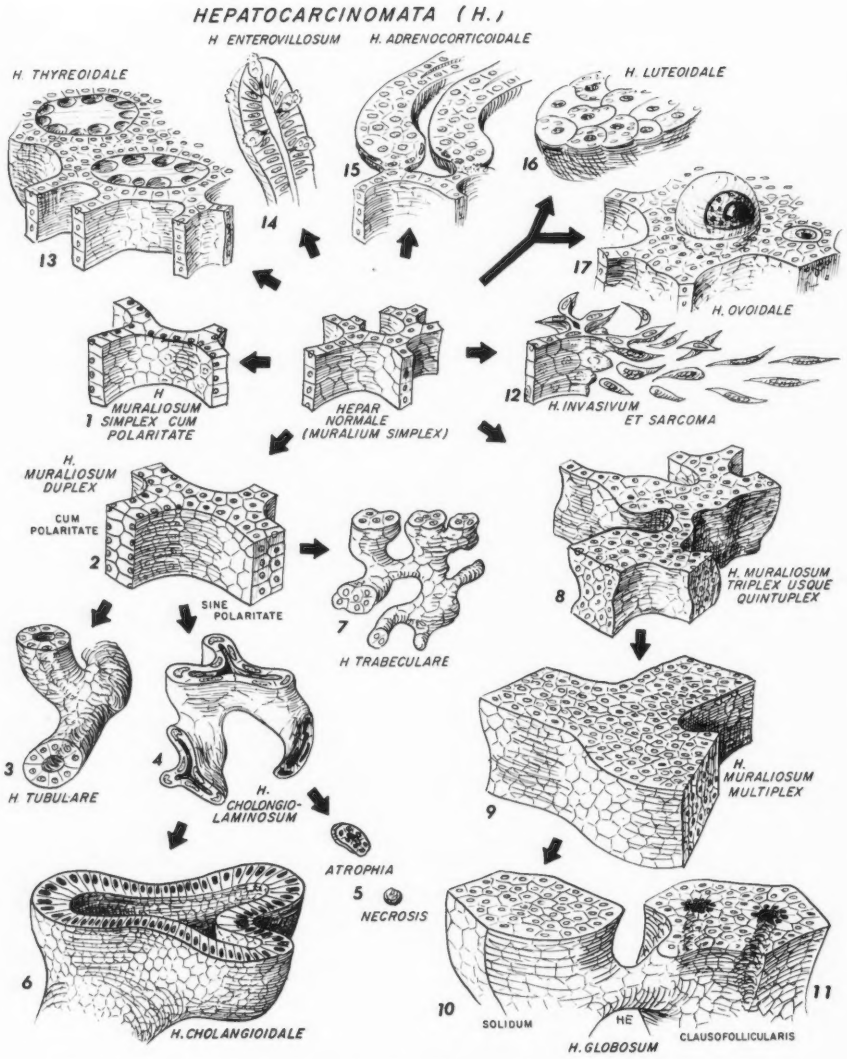


Plate 1. **A graphic presentation of various forms of human primary liver cancer and of their development.**

ing spaces are drawn their normal vertebrate homologues in similar positions. These two charts are taken from a paper entitled *"De morphologia carcinomatis primarii hepatis humani et de eius contextu cum evolutione phylogenetica et ontogenetica"* now in press[17] That paper is the second by the author written in Latin in an effort to re-introduce an international language of science which is so badly needed. As a consequence, the labels on Plates I and II are in Latin, but to facilitate understanding, animal figurines illustrate the species in which the various morphological types occur. Some of the animals and their embryos are drawn as

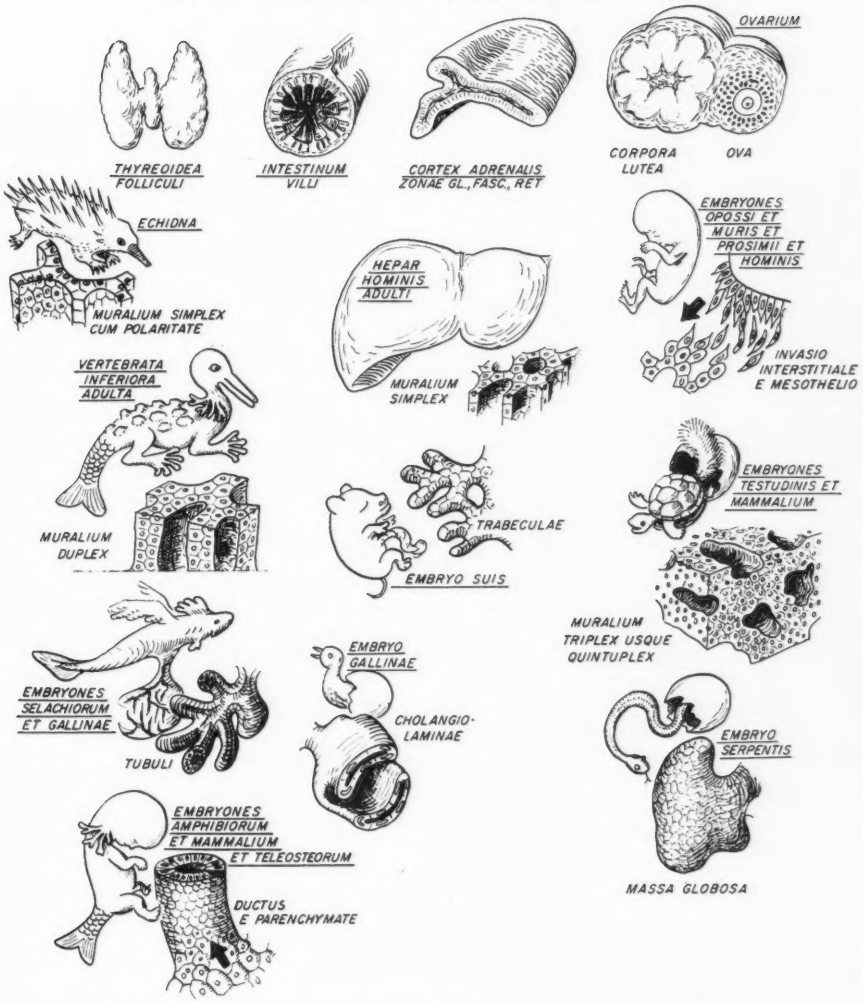


Plate 2. **Homologues among vertebrates and their embryos to be compared with the stereograms on Plate 1.**

chimaerae, when a morpohological type occurs in various groups of vertebrates.

Hepatocarcinogenesis begins from the normal, human liver shown slightly above the middle on Plate I, i.e. from a *muralium simplex*. From there, it can proceed in various morphogenetic directions, as indicated by the arrows. We shall at first proceed horizontally and downward. In one case it was observed at the very beginning of malignancy, that the nuclei of the liver cells had shifted their position from the middle of the cells toward one of their surfaces. A *muralium simplex* with nuclear polarity (1) was thus created, a condition *normally* present in the adult spiny anteater.

Very frequently, a malignancy begins

by cell divisions, so that the liver plates become two cells thick: a *muralium duplex* (2) arises as it is normally present in many adult lower vertebrates. In some cases (right side of block 2) the nuclei remain in the middle of the cells such as in the livers of adult amphibians, and bony fishes. In other cases (left side of block 2) there is nuclear polarity, as in normal adult livers of some lizards, the chick and the wood duck for example.

Two cells thick plates of early hepatocarcinoma can develop in two different directions: The plates can acquire oblong lumina and then break up into tubules (3). This development is the exact opposite of what happens in the shark embryo and in some others (see Table I) in which tubules fuse to form a *muralium duplex;* and it is the same of what happens in lamprey larvae, in which, at first, tubules fuse into a *muralium duplex*. But this *muralium,* at a later stage of development, breaks up into tubules again.[3,18] Or the carcinomatous *muralium duplex* may acquire a continuous, flat lumen, and its cells may flatten and dedifferentiate into ordinary epithelium. (4) This results in the formation of a *muralium* consisting of "cholangiolaminae" so-called because of the resemblance of it to the smallest bile ducts (cholangiola). In this conditon, the hepatocarcinoma has a structure very similar to the early liver primordium of the chick.

The cholangiolaminae frequently degenerate and die (5).

In other cases the flat epithelium of the cholangiolaminae becomes tall columnar, the lumen widens and a cholangioma (bile duct tumor) develops (6). Here we have a phenomenon which is reminiscent of the normal development of bile ducts in many,[7,9,10,11] bony fishes and amphibians, where bile ducts develop from liver cells.

The *muralium duplex* of a hepatocarcinoma can split up into a network of solid cords or trabeculae (7) and thus come to resemble the entodermal portion of the liver primordium of the pig.

The normal *muralium simplex* can, by simultaneous, multiple mitoses, change directly into a *muralium* of plates three to five cells thick (*muralium triplex usque quintuplex*), (8). In this case the cancer is very similar to the embryonic livers of turtles and mammals.

Often the plates of the *muralium* become extremely thick, (9) up to thirty cells thick. Then the tumor has the structure of a *muralium multiplex*. This is, however, not a stable condition and has no counterpart among the vertebrates. Plates of such extreme thickness can not survive long. They may undergo necrosis beginning in the center of the thickest plates. The cells most remote from the blood stream die first.

Often, however, the *muralium multiplex* breaks up into globular masses (10) which are bathed by broadened blood vessels. In this case, the tumor resembles the early liver primordium of garter snakes.

In some cases of liver cell malignancy, the liver cells lose their connection with the *muralium* and, becoming spindle shaped, invade the surrounding connective tissue (12). Their behavior, then, resembles the early liver anlage of mammals, including man, which arises by interstitial invasion.

Since a considerable portion of the human liver parenchyma derives from mesoderm, one is not astonished to find occasional sarcomata (connective tissue tumors) (12), and even osteomata (bone tumors) of hepatocellular origin.[21]

With this, we leave the realm of liver-like liver tumors and we shall glance at the ability of hepatic carcinoma to mimic other organs.

Hepatocarcinomata which contain or even largely consist of typical thyroid follicles, complete with vacuolated colloid are not infrequent.[15,16] They may arise directly from liver cells or sometimes in the interior of *muralia multiplica.*

Liver tumors transplanted into rabbits' anterior eye chambers have developed into typical, intestinal villi with striated border epithelium and goblet cells.[19]

In both cases the malignant liver cells have gone quite a different route; but they have formed typical entodermal structures which are easily recognizable.

There are liver tumors in which a portion of the *muralium simplex* becomes an adrenocortical blastema and produces a large body which would be identified by any histologist without hesitation as adrenal cortex if it were not within the liver and if the direct transformation of typical liver *muralium* into this tumor were not so obvious. It contains all three zones in typical arrangement (15).

In hepatocarcinoma *globosum*, one encounters oblong, crooked and branched lumina surrounded by tall columnar cells. The nuclei of these cells are adjacent to the lumen (11). Such an arrangement of nuclei around a closed lumen, is not known to occur anywhere but in the *typus clausofollicularis* of some human adrenal cortices.[20]

Some liver tumors contain large cell masses which histologically cannot be distinguished from *corpora lutea* (16) of menstruation.

One of the most striking liver tumors was one containing luteoid cell masses. In this tumor an extremely large, spherical cell with spherical nucleus and a conspicuous nucleus was found. This cell resembled in every respect an almost mature oocyte (17). In the same tumor all stages of transition from typical liver cells to typical eggs could be seen. The transitions consisted in general enlargement of the entire cell, its nucleus and its nucleolus.

The adrenoid and ovaroid hepatocarcinomata can be explained because a considerable part of the human liver derives from the mesothelium which is also the source of the adrenal cortex and of the ovary.

Thus we can see that primary liver cancer cells though having a large degree of freedom to develop in various directions, always remain morphologically faithful to their own two germ layers and in most cases, to the liver of vertebrates. The liver-like liver tumors are not only more frequent than thyroid, adrenoid, enteroid and ovaroid tumors, but they appear to be more important from the standpoint of evolution.

They demonstrate that all vertebrates are very closely related, that one vertebrate has within itself morphogenetic potentialities of almost all other vertebrates.

It appears that the morphogenetic homologues of human primary liver cell cancer are one of the strongest pieces of evidence of our close affinity and relationship to and descendence from lower vertebrates.

REFERENCES

1. Elias, Hans, 1948: Do liver cords exist? Anat. Rec. *100*:655.
2. ——— 1950: Discovery by Illustration. Sc. Monthly. *70*:229-232.
3. Elias, Hans and Herbert Bengelsdorf, 1952: The structure of the liver of vertebrates. Acta Anat. *14*:297-337.
4. Hickey, Joseph and H. Elias, 1954: The structure of the liver of birds. Auk *71*:458-462.
5. Elias, Hans, Edwin Spanier, Albert Sokol and Alexander Lazarowitz: Contributions to the Geometry of sectioning I, II, III, and IV: 1953-1955. Z. Wiss. Mikrosk. *61*:213-221; *62*:20-31; *62*:32-40; *62*:417-426.
6. Elias, Hans, 1952: The geometry of cell shape and the adaptive evolution of the liver. J. Morph. *91*:365-388.
7. Elias, Hans, 1955: Origin and early development of the liver in various vertebrates. Acta Hepatologica *3*:1-56.
8. Lipp, Walther, 1952: Die Entwicklung der Parenchymarchitektur der Leber. Verh. Anat. Ges. 50. Vers. Marburg: 241-249.
9. Lewis, Frederic T., 1912: The development of the liver. In: Keibel and Mall: Manual of Human Embryology, Phila. and London: 403-428.
10. Horstmann, Ernst, 1939: Entwicklung und Entwicklungsbedingungen des intrahepatischen Gallengangsystems. Roux's Arch. *139*:364-392.
11. Elias, Hans, 1953: Embryonic diversity leading to adult identity, as expressed in the development of the livers of vertebrates. Anat. Rec. *177*:556-557.

12. Sewertzoff, A. N., 1928: Ueber die Beziehungen zwischen der Ontogenese und der Phylogenese der Tiere. Jenaische Z. Naturwiss. 63 (neue Folge, 56): 51-180

13. Simpson, George G., 1949: The meaning of evolution. Yale Univ. Press, New Haven.

14. Elias, Hans and Hans Popper, 1956: Histodynamik der Leberzirrhose. Acta Hepatologica, 4:1-27

15. Edmondson, H. A. and P. A. Steiner, 1954: Primary carcinoma of the liver. Cancer. 7:462-503.

16. Elias, Hans, 1955: Human hepatocarcinoma and the comparative embryology of the vertebrate liver. J. Nat. Cancer Inst. *15*:1451-1462.

17. ..... 1957: De morphologia carcinomatis primarii hepatis humani et de eius contextu cum evolutione animalum vertebratorum. Acta Hepatologica 5:1-18.

18. Bengelsdorf, Herbert and Hans Elias, 1950: The structure of the liver of Cyclostomata. Chicago Med. Sch. Quarterly *12*:7-12.

19. Bensley, Sylvia H., 1956: Liver tumor cells in the anterior chamber of the eye. Anat. Rec. *124*:451.

20. Elias, Hans, and John E. Pauly, 1956: The structure of the human adrenal cortex. Endocrinology *58*:714-738.

21. Allison, R. M. and Willis, R. A., 1956: An ossifying embryonic tumor of an infant's liver. J. Path. Bact. 72:55-159.

FUNDAMENTAL ACTIONS OF DIGITALIS

JAY A. SMITH, Ph.D.*

OUTLINE

I. Introduction

For an understanding of the fundamental actions of digitalis, a complete understanding of two important processes is necessary: first, the elaborate mechanisms for the formation, storage, and utilization of energy must be known; and second, the basic processes of muscular contraction must be clearly understood. Since the ultimate details of both of these processes are still not entirely clear it would seem, *a priori*, that the details of the mechanism of action of digitalis would also be obscure. Such is the case. However, a vast amount of worthwhile research has been published since the monumental review by Wollenberger[143]. It is the purpose of this review to assemble this recent literature, and it is the intention of the reviewer to editorialize on those occasions when it is appropriate to interpret the aggregate meaning of the articles that will be cited.

Any extensive discussion of digitalis must include aspects of its therapeutic and toxic effects. In this review, articles will be cited that bear on the former, and only those articles dealing with toxicity will be cited when they contribute to an understanding of the mechanism of therapeutic doses.

The term "digitalis" as used hereafter

*Associate Professor, Department of Physiology and Pharmacology, The Chicago Medical School.

will refer to any material that has the action of digitalis. Mention of a specific preparation will be made only when required.

Two great bodies of information must be reconciled in a discussion of the fundamental actions of digitalis. On the one hand is the vast volume of information that establishes the fact that digitalis *is of benefit* in certain types of heart disease[44], that it accomplishes this, at least in part, by improving the strength of the heart beat, and that its effects are reflected in an improvement of contraction of the heart. On the other hand is the almost equally vast volume of information, often conflicting, frequently difficult to interpret and even more difficult to apply to any unified theory of action, that deals with the *way* in which digitalis exerts its beneficial effects. This review will assemble and attempt to classify information from the latter realm.

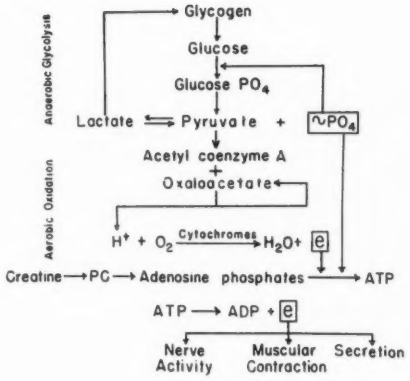


Figure 1

Simple scheme of carbohydrate metabolism. Symbols and abbreviations PO_4, high energy phosphate; e, energy PC, phosphocreatine; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

II. Actions of Digitalis

Digitalis seems to exert its greatest effects on the hypodynamic heart. But, as will be shown in detail, it also exerts well defined effects of one sort or another, on a variety of tissues of the body: it has certain effects on skeletal muscle, especially on ischemic muscle; it affects respiration of brain cortex and kidney; certain effects are demonstrable on erythrocytes; and finally some effects can be demonstrated on mitochondria from a variety of cells.

A. *Localization of digitalis.* The first problem to be settled might be the site of localization of digitalis: where does it go in the body and in the cell? Bine *et al*[9] indicate that parenteral injection in the rat results in distribution of digitalis to various organs of the body with the possible exception of the brain; they show that the heart does not accumulate digitalis. Okita *et al*[101], using digitalis from plants grown in an atmosphere containing radioactive carbon as carbon dioxide, show that the heart does not seem to have any special affinity for the drug, and that the liver is the site of maximum destruction of the material. Friedman *et al*[38, 130] show that digitoxin is found largely in the supernatant fluid after centrifugation of cell homogenates, and only a small amount is found in the mitochondria; they hypothesize that the action of digitoxin is not on enzyme systems which[19] are contained in mitochondria, but rather on the contractile elements of the cell. Harvey and Pieper[53] investigate the intracellular distribution of digitoxin made radioactive with C^{14} and find that it is most concentrated in the "debris," is less concentrated in the nuclear and in the mitochondrial fractions, and is least concentrated in the aqueous fraction.

From these reports it would seem that the heart has no particular affinity for digitalis, and that digitalis is not localized in mitochondria.

B. *Effects of digitalis on carbohydrate metabolism.* Many investigators[14, 33, 34, 35, 58, 59, 61, 66, 78, 80, 81, 110, 117, 127, 128, 144, 148] indicate that digitalis increases respiration. Some[56, 80] contend that it decreases respiration and some[8, 87, 110] indicate that digitalis modifies the respiratory quotient. Apparently digitalis has some effect on metabolism.

1. *Review of carbohydrate metabolism.* For the purpose of this article, a highly

simplified scheme of carbohydrate metabolism is presented (Fig. 1).

Anaerobic glycolysis may be regarded as the conversion of glycogen to pyruvate. Although some high energy phosphate is required for the formation of glucose phosphate, the net result is the formation of high energy phosphate. The high energy phosphate is stored as adenosine triphosphate (ATP).

Under anaerobic conditions, the pyruvate may be converted to lactate. Then, under aerobic conditions, the lactate may be converted back to glycogen, or it may be re-converted to pyruvate. Pyruvate is converted, under aerobic conditions, to acetyl coenzyme-A, and it, plus oxaloacetate, is converted to oxaloacetate and hydrogen ions. These hydrogen ions and oxygen are converted to water by the cytochromes, with the liberation of energy (e); this energy makes possible the synthesis of ATP from various adenosine and creatine phosphates.

When ATP is decomposed with the liberation of the terminal high energy phosphate, energy is released, which can motivate muscle contraction, nerve transmission, secretion, and various other activities.

References[6, 48, 76, 84] are presented which review the general aspects of this complex problem.

2. *Action of digitalis.* Numerous observations have been recorded that deal with the possible sites of action of digitalis in the scheme given above.

a. *Effects of anoxia.* First, and possibly of basic importance, are various reports relating oxygen and anoxia to the response to digitalis. Lundin and Strom[92] point out the essential need of oxygen for restoration of the hypodynamic heart toward the normal, with strophanthin. Meier and Tripod[96] contend that full saturation of perfusion fluid with oxygen is necessary for maximum effects of small doses of strophanthin.

b. *Anaerobic glycolysis and aerobic oxidation.* Wollenberger[146] shows that ouabain caused increased $C^{14}O_2$ formation from labeled glucose, although attended by reduced glucose uptake and reduced glycolysis. Furthermore, there was an increase in uptake of labeled lactate and an increase in respiration in the presence of the latter. Hisada and Nakashima[61] show that although k-strophanthin caused a great increase in respiration, glucose was not necessary for this increase. Segre[124], using guinea pig muscle, indicates that ouabain at a concentration of 10^{-6} caused an increased production of pyruvate with a decrease in glycogen, glucose-1-phosphate and lactate. At higher concentrations, ouabain caused increased production of lactate and a decrease in pyruvate. Segre[123] found similar results with red blood cells, and hypothesizes that the action of digitalis is on enzyme systems, where it may act as an H-ion carrier. But Wollenberger[145] shows that aerobic phosphorylation was not affected by ouabain. Langemann and others[80] show that ouabain increased respiration of cat heart slices but failed to affect oxidative or phosphorylative capacity of mitochondrial preparations, and concludes that "the effects of ouabain on intact heart cells are mediated by some other means than a direct action upon oxidative enzymes" (p. 280). Reiter and Barron[114] found that digitalis preparations had no effect on anaerobic glycolysis of heart slices, on oxidation of lactic and acetic acid in heart sections and homogenates, on oxidative phosphorylation in homogenates, or on oxidation of phosphoglyceraldehyde and lactic acid with purified enzyme systems.

Helmreich[55] and Segre[125] indicate that digitalis preparations have no effect on the cytochrome c or cytochrome oxidases.

Parenthetically, Burdette[15] found that human heart muscle did not convert digitoxin labeled with radioactive C^{14} to $C^{14}O_2$, indicating that digitoxin acts catalytically.

In summary of this section, it appears that digitalis may affect the overall results of carbohydrate metabolism, but not via specific enzyme systems.

c. *Source of energy.* Ellis[29], using the frog heart, shows that if glycolysis is blocked by iodoacetate (leaving aerobic

oxidation intact) ouabain still produces a positive inotropic effect. If aerobic oxidation is blocked with fluoroacetate or by anoxia (leaving anaerobic glycolysis intact) ouabain still can produce a positive inotropic effect, but if formation of high energy phosphates is blocked by dinitrophenol (even though glycolysis and aerobic oxidation remain intact) ouabain now does not produce a positive inotropic effect. In other words, if formation of high energy phosphates is possible from any available energy source, ouabain can produce a positive inotropic effect. These experiments are representative of many which indicate the importance of high energy phosphate metabolism for a digitalis effect.

d. *Phosphorylation.* Since phosphorylation with the resultant formation of high energy phosphates seems to be an end product of metabolic activity, it seems plausible that the activity or the quantity of the components involved in phosphorylation might vary under certain conditions such as heart failure, anoxia, abnormalities of carbyhydrate metabolism, etc.

Wollenberger[142] produced failure with anesthetics in a heart of a heart-lung preparation, and reports an increase in phosphocreatine but no change in ATP. Greiner[46], using improved analytical methods, found that in papillary muscle strips made hypodynamic with anoxia, there was a decrease in both phosphocreatine and ATP, and in muscles becoming hypodynamic spontaneously there was no change in phosphocreatine but a decrease in ATP which could be restored toward normal with ouabain. Rebar, Rebar and Proctor[112] produced failure of the right ventricle in a dog heart, and report a significant decrease in ATP in that organ and a restoration of ATP toward normal by digitoxin. Erzina[32] shows that hearts stopped by being made anoxic could contract temporarily when ATP was added, and Lichtneckert and Straub[86] restored hearts made hypodynamic with quinidine by adding ATP.

Digitalis itself may have some effect on phosphorylation. Wollenberger[145] indicates that there is no change in phosphocreatine when digitalis preparations are given in doses causing positive inotropic effects but there is a depletion of phosphocreatine when digitalis preparations are given in doses causing toxic effects. Hermann[59] reports that ouabain does not affect phosphocreatine; Greiner[46] reports no change in phosphocreatine but a decrease in ATP with ouabain. Kimura[70] gave digitoxin to rats for three days in doses that produced no toxic effects, and reports that the treatment did not alter the phosphocreatine or the ATP content of the hearts. Alstrom[2], using radioactive phosphorus, discovered that in the heart, digitoxin in sub-toxic doses increased phosphorus metabolism and in toxic doses had no effect. In the liver, digitoxin in sub-toxic doses had no effect on phosphorus metabolism but toxic doses decreased it.

e. *Skeletal muscle.* Certain parenthetical remarks might be appropriate at this point pertaining to skeletal muscle. Clinically, at least[44], digitalis has very little effect on normal hearts. Digitalis also has little effect on skeletal muscle[22]. However, when skeletal muscle is made ischemic (Pardo, del Pozo *et al*[22,106]), digitalis increases the strength of its contractions. To this reviewer's knowledge, no data comparable to those of Greiner[46] are available for skeletal muscle. It is easy to hypothesize that anoxia of skeletal muscle produces changes comparable to those occurring in failure of cardiac muscle, possibly comparable to those changes in the various phosphates noted by Greiner[46]. This might render skeletal muscle susceptible to the action of digitalis.

To summarize the evidence dealing with phosphate metabolism; it appears most likely that various hypodynamic conditions are accompanied by alteration in the levels of various phosphates, particularly ATP, that these changes may be restored toward normal by proper doses of digitalis, but that in some cases, usually within the toxic dosage range, digitalis itself may affect various phosphates.

f. *Methods of action of digitalis.* The next question that must be resolved is this: How does digitalis produce changes

in phosphates? Kimura and DuBois[72] present a table showing that digitoxin inhibits the ATP-ase activity of rat heart muscle. Proctor, Rebar and Rebar[108] show that digitoxin can inhibit both ATP-ase and ATP-deaminase of heart muscle. Now myosin, according to Engelhardt and Ljubimova[30] can act as an ATP-ase, splitting off the terminal phosphate, and, according to Banga and Josepovits[4] as an ATP-deaminase, splitting off the 6-amino group of adenosine. Engelhardt[31] agrees, and adds that myosin is a complex of two proteins, one, associated with ATP-ase activity, which combines with actin; the other, associated with ATP-deaminase activity, which does not combine with actin. Hermann and Josepovits[60] had previously showed that actin-free myosin was capable of deaminating adenylic acid. Edman[24] describes some of the properties of myosin-ATP-ase and displays experiments showing that g-strophanthin inhibits this ATP-ase. Munchinger[99] contends that digitalis enhances the activity of ATP in heart muscle homogenates, probably by inhibiting the ATP-ase.

Since the ATP-ase activity of myosin is linked to the presence of free-SH groups[132], the work of Bertelli and Mussini[7] is pertinent since they show that strophanthin decreases the quantity of these groups in heart muscle preparations.

Proctor, Rebar and Rebar[109] reveal that digitoxin is capable of forming a peroxide with dissolved oxygen and that the peroxide is a stronger inhibitor of ATP-ase than digitoxin itself.

These results appear to be in agreement in a field of research where agreement is not the rule. They indicate that digitalis may serve as an inhibitor of various ATP-ases, so that ATP, where it is deficient (Chen and Geiling[17]; Greiner[46]), could be preserved.

As usual, certain additional results have been described. Edman[25] shows that ouabain may stimulate myosin-ATP-ase, or may inhibit ATP-ase in a muscle extract containing both water soluble and myosin-bound ATP-ase. Helmreich and Simon[57] show that the effect of k-strophanthoside on ATP-ase is slight. This state of conflict seems resolved by Read and Kelsey[111] who show that digoxin enhances the action of myokinase (which might have been a complicating impurity in some of the work cited previously) and may also suppress the myokinase inhibition of myosin-ATP-ase.

Thus, according to the conditions that prevail, such as the method of extracting the muscle preparations, digitalis can in effect, either inhibit or facilitate the inactivation of ATP-ase.

To summarize to this point, it seems that digitalis preparations can preserve ATP, especially in hypodynamic hearts, probably by inactivation of various ATP-ases.

These results are compatible with many other observations which show that as long as energy is available for phosphorylation, digitalis will exert a positive inotropic effect, but that if phosphorylation is blocked, digitalis will no longer have a positive inotropic effect (Ellis[29]). Other reports have an indirect bearing on this hypothesis. Lee[83], using metabolic poisons on cat heart muscle while simultaneously measuring contraction and oxygen consumption, shows that iodoacetate, which blocks glycolysis, did not alter oxygen uptake but reduced contraction. Fluoroacetate, which blocks aerobic oxidation, reduced both oxygen uptake and contraction, whereas dinitrophenol, which blocks phosphorylation, increased oxygen uptake but reduced contraction. Ellis[28] shows that epinephrine produced a positive inotropic effect after iodoacetate and fluoroacetate but not after dinitrophenol, again pointing out the importance of a source of energy and of phosphorylation for muscular contraction. Lundin and Strom[92] show that hypodynamic hearts may be restored toward normal by strophanthin, except when made hypodynamic by anoxia. Wollenberger, in a series of papers[142, 145, 147], asserts that in the failing heart there exists an impairment of utilization of high energy phosphates and that digitalis improves such utilization.

3. *Relation of digitalis to "uncoupling"*

agents. Certain interesting problems in cardiac physiology are posed by observations on the action of "uncoupling" agents, such as dinitrophenol. "Uncoupling" agents (Brody[13]) are materials which dissociate phosphorylation and oxidation, and in general, inhibit phosphorylation while promoting oxidation.

Digitalis is not an "uncoupling" agent *per se* when used with mitochondrial preparations[80] or with homogenates[114]. It is well established that dinitrophenol (DNP) produces contracture of skeletal muscle accompanied by a decrease in phosphocreatine and ATP[5]. Hunter[65] believes that DNP activates an ATP-ase and thus reverses the reactions involved in ATP formation. Grisolia[47] shows that in mitochondria, digitalis potentiates the uncoupling action of DNP. Rothlin *et al*[118] find that a digitalis preparation exerts a cardiotonic effect after moderate DNP poisoning, but not after severe DNP poisoning. Wollenberger and Karsch[147] indicate the ouabain and DNP individually did not affect the ATP content of guinea-pig hearts but that together, they reduced the ATP content to half of the control level.

It will be readily appreciated that the nature of the relationship between the actions of DNP and digitalis awaits clarification.

4. *Effects of digitalis on oxygen consumption.* In a perusal of the literature pertaining to the present topic, many articles are found dealing with the oxygen consumption of the heart and other tissues under the influence of digitalis. The interpretation of the results of such experiments is frequently difficult, since changes in the rate of oxygen consumption are not necessarily specific, but may be due to a wide variety of known and to an indeterminable number of unknown factors.

a. *On the heart.* Wollenberger[143] and Hermann[59] present clear-cut evidence showing that ouabain (2×10^{-7} Molar) produced an increase in the oxygen consumption of heart slices and at higher concentrations (10^{-6} to 3×10^{-7} M) there was an increase followed by a decrease. Finkelstein[33,34] obtained similar results with different concentrations of scilliroside. Quite similar results were also obtained by Rothlin and Schoelly[117] who, in addition, show that hearts from rats given 0.02-0.05% of the LD_{100} (approximately the therapeutic dose) of digitalis preparations exhibited an elevated oxygen consumption. Fischer *et al*[35] demonstrated an increased oxygen consumption of heart slices. Burdette[14] shows that the oxygen consumption of human heart slices was increased by lanatoside C. Ransom and Loomis[110] show that as the concentration of ouabain is increased, the oxygen consumption of rat heart auricle under tension, increased, with a maximum at about 10^{-6} M. Lee[81], using an ingenious apparatus of original design, shows that ouabain increased oxygen consumption of cat papillary muscle, but only after a latent period and at a time when contracture and various arrhythmias developed. Hisada and Nakashima[61], Hermann *et al*[58] and Hunziker[66] report increased oxygen consumption with a variety of conditions after administration of various digitalis preparations.

But Helmreich and Nowy[56] report that k-strophanthin, *in vitro* and *in vivo*, reduced the oxygen consumption of heart muscle. Reiter[113] indicates that both contractile energy and oxygen consumption decreased with time and that strophanthin prevented the latter. Bianchi[8] shows that strophanthin increased carbon dioxide production and thus raised the respiratory quotient, and Levinson and Aisner[85] show that the oxygen consumption of non-contracting muscle was not altered by digitoxin.

Some reports indicate that the increase of oxygen consumption occurred with toxic doses of digitalis. Wollenberger[144] gave ouabain intravenously to dogs, excised the hearts at the time of onset of extrasystoles, and found that the oxygen consumption of such hearts was higher than that of normal hearts. Smith *et al*[127,128], using the embryonic chick heart in the cartesian diver, found an appreciable increase in oxygen consumption, but only at concentrations that also produced some degree of arrhythmia.

b. *Other tissues.* The increase in oxy-

gen consumption produced by digitalis is not confined to the heart. Wollenberger[141] and Wollenberger and Wahler[148] show that ouabain increased the oxygen consumption of brain cortex. Frey[37] shows that strophanthin in the proper concentration produced an increase in oxygen consumption of kidney slices and mashes, but not of homogenates. Recently, mitochondrial preparations have become available by selective centrifugation. Langemann and others[80] obtained an increase in oxygen consumption by adding ouabain to cat heart slices, but no increase by adding ouabain to mitochondrial preparations. Lamprecht[78], on the other hand, found that strophanthin increased oxygen consumption of mitochondria from liver, and of sarcosomal material from insufficient hearts, but found that it produced no increase with sarcosomal material from normal hearts.

Accounting for the variation observed in the response of tissue oygen consumption to digitalis is largely speculative. Correlative evidence might aid in explaining the variance of observations. Clark and White[18], long ago, showed that the oxygen consumption of the heart is proportional to the diastolic volume. Lee[82], indicates that muscular contraction and oxygen consumption under the influence of epinephrine are parallel. Furthermore, digitoxin did not affect the oxygen consumption of non-contracting hearts[85]. Although ouabain[110] increased the oxygen consumption of heart muscle under tension, it did not alter the oxygen consumption of hearts not under tension; likewise[81] ouabain increased the oxygen consumption but only simultaneous with contracture. It would seem plausible then, to assign an important role in affecting oxygen consumption. to the degree of muscular contraction, contracture, or activity. In addition, as mentioned previously, poisoning various metabolic pathways, even with simple (and ubiquitous) anoxia[39, 103] may interfere with the mechanical or metabolic response of heart muscle to digitalis. It is quite likely that the respiratory response to digitalis may depend on the integrity of efficient metabolic pathways.

c. *Meaning of the increased oxygen consumption.* The meaning of the increase in oxygen consumption induced by digitalis is also highly speculative. The increase might represent an increase in permeability of the cell membrane to substrates as Wollenberger[141] suggests. Or, the increase might be a reflection of improved oxidation as a possible result of improved phosphate metabolism. Or, in some cases, at least, it might represent the result of an increased ability of the muscle to contract. Further experimentation seems justified.

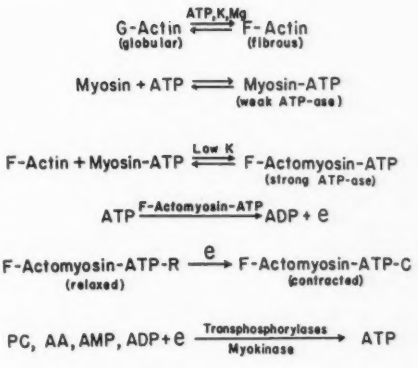


Figure 2

Simple scheme for muscular contraction. Symbols and abbreviations are the same as in Fig. 1, and in addition: AA, adenylic acid; AMP, adenosine monophosphate.

C. *Muscular contraction.* A basic and undeniable property of digitalis is that it exerts an effect on contraction of muscle.

1. *Review of muscle contraction.* An attempt to present a complete scheme of muscle contraction in a review of this nature would be absurd, in view of the welter of polemics in this field. Therefore a simplified scheme is presented (Fig. 2) that answers most of the requirements in explaining successive muscle contractions and relaxations. The saying that "Many arguments generate more heat than light,"[36] certainly applies to muscle contraction in more ways than thermodynamically. The reader is urged to read[23, 40, 132, 133] and form opinions for himself.

In the resting muscle (see Fig. 2) G actin (globular actin) is organized into

F-actin (fibrous actin) under the influence of ATP, magnesium ions and potassium ions[132,133]. Also in resting muscle, myosin is organized with ATP[135] to form a complex that is only a weak ATP-ase. Magnesium ions reduce the ATP-ase activity of this complex. In addition, in the resting muscle the potassium ion concentration is held at a higher level than at the exterior, by the so-called "potassium pump" (a descriptive name void of all implications as to its mechanism of action). And finally, in the resting muscle, various enzymes, such as myokinase and at least two transphosphorylases, aid in maintaining an optimum quantity of ATP.

When a stimulus, such as an electric current, an injury, or a normal stimulus from a nerve or a pacemaker reaches the muscle, the following may be expected to take place: The selective permeability of the membrane (another non-implicating name of a phenomenon having the same function as the "potassium pump") might momentarily disappear, and potassium would leak out of the cell[49,121,122,140]; the decrease in the potassium ion would favor the reaction between actin and myosin forming actomyosin; the magnesium ion would now reverse its effects and would enhance the ATP-ase activity of the newly formed actomyosin-ATP complex. This might be expected to break down ATP (see [79,97,98]), to release energy (see [136]), which would alter the actomyosin itself, into a shortened form.

ATP serves yet another purpose as a "plasticizer"[133,135]; when ATP is present, actomyosin is plastic. When ATP is absent, actomyosin becomes stiff and rigid as in contracture resulting from DNP[5], rigor mortis, and in the contracture of excess muscular fatigue.

The entire process of contraction can be regarded as a process in which one reaction (conjugation of actin with myosin), under the influence of a lowered potassium content, not only produces the contractile element actomyosin, but also endows that same element with the ability to release, from ATP, the energy for its own contraction.

Relaxation may be regarded as a reversal of the above processes[12], in which, under an increased potassium content, contracted actomyosin is relaxed by dissipation of the energy that had been produced, and simultaneously, its ATP-ase activity and its contractile powers are lost by its dissociation into actin and myosin.

Some contend[101] that the release of energy from the breakdown of ATP occurs during relaxation.

2. *Action of digitalis on muscular contraction.* Digitalis has some effect on several of the steps described above. Horvath, Kiraly and Szerb[64] indicate that digitalis polymerized actin from dog hearts but not from dog skeletal muscle. Snellman and Gelotte[129] point out that digitalis inactivated a deaminase, thus allowing ATP to polymerize actin. Edman[27] indicates that in the presence of calcium, digitalis enhanced the contraction induced by ATP in glycerine extracted muscle fibers and in beef heart extracts[24].

3. *Action of digitalis on muscle models.* The preparation of actin, myosin, actomyosin, and other materials involved in muscular contraction, in relatively pure form, now seems a matter of cook-book simplicity[132]. Mallov and Robb[93] show that digitoxin enhanced the contraction of actomyosin threads induced by ATP. Bowen[10] describes some of the properties of such a contraction, and states[11] that digitoxin increased the degree and rate of shortening of myosin B (actomyosin) threads from skeletal muscle, and concludes that "since no carbohydrate metabolism is known to occur in myosin B threads, digitoxin must produce its effect by altering the contractile proteins or the union between ATP and myosin."

The logical result of efforts on precipitated actomyosin is the work of Hayashi[54] who describes a method for producing films of actomyosin having sufficient strength for mechanical experimentation. Robb and Mallov[116], using such films, demonstrate that ouabain increased the speed of shortening as well as the degree of shortening at various tensions, when ATP was added.

The precise meaning of these unequivocal results must await further experimentation; they fit nicely into the hypothesis that digitalis functions as an inhibitor of ATP-ase.

4. *In vitro effects of digitalis.* New approaches to *in vitro* effects of digitalis on muscle contraction have recently appeared. The work of Lee[81] has already been mentioned: digitalis produced a contracture of papillary muscle concurrent with increased metabolism and appearance of arrhythmias. Whitehorn[137] indicates that digitalis, among other factors, favored development of tetanus and summation in frog hearts. Luisada and Weiss[91] show that ouabain shortened the resting length of cardiac fibers and decreased the height of their contractions. Matsuoka and Saunders[95], using strips of muscle from rat ventricles, produced hypodynamic conditions by rapid stimulation, and were then able to restore the strips toward normal for a time, with ouabain.

5. *Effects of digitalis on "treppe."* Hajdu[49], Hajdu and Szent Gyorgyi[51] and Porro[107] show that digitalis eliminated "treppe."

These experiments, in the aggregate, could be interpreted to mean that digitalis, in intact hearts, in muscle strips, in extracted muscles, and in muscle models, facilitates contraction, favors contracture, eliminates "treppe," and possibly inhibits relaxation.

D. *Ions.* Since the days of Ringer[115] the role of ions in cardiac function has been a subject of considerable investigation. In more recent years, development of techniques for the quantitative measurement of ions has led to new advances in this field. Fortunately, the relation between ions and the actions of digitalis has been explored with considerable success.

1. *Potassium.* Of the common ions, potassium has received most attention.

a. *Potassium in the heart.* Potassium exerts an influence on, and is influenced by the action of digitalis in many tissues. The heart is one.

(1) *Relation between potassium and digitalis.* The effect of potassium on the action of digitalis seems well established[44]; Baker[3], for example, shows that an increase in potassium ion increased the LD_{50} of ouabain. Lown and others[88, 89, 90], in a series of papers, show that the severity of digitalis intoxication varied inversely with the potassium concentration of various body fluids. Page and Real[105] show that decreasing the serum calcium or increasing the serum potassium reduced arrhythmias due to ouabain.

(2) *Relation between digitalis and potassium.* The effects of digitalis on potassium ion concentration have received recent attention. Greef[45] shows that strophanthin, in rats, increased the urine volume, the excretion of sodium, the excretion of potassium, that it increased serum potassium, decreased serum sodium, decreased muscle potassium and increased muscle sodium. Aikawa and Rhoades[1] show that digitoxin, given chronically or in a single dose, reduced tissue potassium. Hajdu[49] indicates that the height of contraction and the release of potassium were parallel, that potassium was released during contraction and re-entered the cell during rest, and that digitalis prevented the re-entry of potassium into the cell. Holland and others[63] show that lanatoside C caused a loss of potassium from the hearts of guinea pigs, which was proportional to the potassium concentration of the external fluid. Holland and Dunn[62] conclude that "drugs that modify . . . the functional state of a cell . . . affect rather profoundly the permeability of the intact cell to Na and K ions" (p. 489). Among such drugs is ouabain, which causes a loss of potassium. Conn[20] furnishes elaborate proof of the thesis that the "major action of digitalis is the partial inhibition of potassium transfer into the myocardial cell" (p. 548). Schreiber[122] presents neat graphs proving that intracellular potassium exists in two compartments which exchange at different rates. Ouabain inhibits entrance into the cell of that potassium exchanging at the slower rate. Schatzmann and Witt[121] show that strophanthin caused a net loss of potassium

from the cell, resulting from interference with the sodium-potassium pump and with potassium outflow during the falling phase of the action potential.

On the other hand, Gertler *et al*[42] were unable to demonstrate that digitoxin produced any significant alteration in the potassium content of rabbit hearts.

b. *Potassium in other tissues.* Wollenberger and Wahler[148] show that strophanthin caused 100% inhibition of potassium uptake by brain slices. Glynn[43], Kahn *et al*[68], and Schatzmann[120] all show that digitalis inhibited the transport of potassium into erythrocytes. Johnson[67] shows that ouabain and strophanthidin (which have cardiac actions) inhibited the net transport of potassium into frog sartorius muscle; on the other hand, dihydrostrophanthidin (which has only a very weak cardiac action) did not inhibit potassium transport. This is interpreted to indicate that potassium transport is fundamental to digitalis activity.

c. *Summary of digitalis-potassium relationship.* At this point the reader's attention should again be focused on a phenomenon discussed previously: "treppe" is a phenomenon in which "every contraction leaves behind a more favorable condition that it has found"[50] (p. 167), and treppe disappears (or the most favorable condition is reached) when potassium is reduced or lost[49, 50, 102, 107]. Is it coincidence or more than coincidence that digitalis has many of the effects that are produced by a loss of potassium and that digitalis causes a loss of potassium?

An interesting aside at this point is brought out by the report of Manery *et al*[94] who show that insulin and lactate increased both oxygen consumption and potassium uptake by frog skeletal muscle. This could be interpreted as support of the contention that potassium uptake is related to conditions of metabolism, such as oxidation within the cell.

The digitalis-potassium relationship can be summarized as follows: First, increasing the concentration of potassium decreases the toxicity of digitalis. Second, potassium moves from the cell during cellular activity and is restored to the cell during cellular quiescence. Third, digitalis causes a loss of potassium from the cell.

2. *Calcium.* A mutual relationship between digitalis and calcium exists. Harvey and Peiper[53] show that deviation of calcium from a certain normal concentration tended to shift digitoxin from the particulate and cellular fractions to aqueous fractions of cellular homogenates. Salter *et al*[119], using the frog heart, show that if the contraction is suppressed by lack of calcium, it may be restored with digitalis. Wilbrandt[138] presents a similar finding and concludes that the prime action of digitalis is on ion transport, particularly of calcium, to actomyosin. Edman[27], using glycerine extracted muscle fibers, shows that the contraction resulting from ATP could be increased if calcium were present. Matsuoka and Saunders[95] report that calcium can both increase and decrease the positive inotropic effect of ouabain, depending upon its concentration. Kutschera-Aichberger[77] indicates that the inotropic effect of strophanthus is intensified by calcium.

Wilbrandt[138, 139] states that calcium is lost from the cells of the frog heart and that digitalis reduces this loss significantly.

3. *Sodium.* Schatzmann[120] and Johnson[67] note that digitalis inhibited the net movement of sodium from the cell. It would also seem, from these authors' reports, that the movements of sodium are principally a reflection of the movements of potassium under the influence of digitalis.

E. *Acetylcholine and cholinesterase.* In clinical usage, one of the most commonly noted effects of digitalis therapy is a slowing of the heart rate. This may well be reflex in nature, due possibly to lowered venous pressure. Many accounts appear in the literature attributing anticholinesterase properties to digitalis. Kimura[71] indicates that digitalis did not affect the cholinesterase activity of the medulla, and Konzett and Rothlin[74, 75] say that digitalis had no direct effect on the cervical ganglion of the cat but did potentiate acetylcholine. Chatterjee[16] mentions that ouabain potentiated the effects of

eserine. Holland *et al*[63] show that lanatoside C seemed to decrease cholinesterase activity but was dependent on potassium and acetylcholine concentration. Proctor and others[108] hypothesize that digitoxin inhibits acetylcholinesterase. Haltori[52] finds that inhibition of cholinesterase by various digitalis preparations existed but was too weak to account for the effects that are observed on the heart. Shinohara[126] finds much more cholinesterase in the auricle than in the ventricle, that cholinesterase was blocked by digitalis in large sub-toxic doses, and that the digitalis blockage was enhanced by removing the liver from circulation.

Nagayama[100] contends that strophanthin did not increase the activity of cholinesterase but did increase the synthesis of acetylcholine. In contrast, lanatoside C increased both activity of cholinesterase and the synthesis of acetylcholine. Danielopolu[21] proposes a sweeping theory that the action of digitalis depends on inactivation of cholinesterase and of adrenolytic agents.

F. *Electrical phenomena.* Woodbury and Hecht[149] maintain that various digitalis preparations had no effect on the membrane resting potential and action current, but shortened the time of onset of recovery, all without affecting mechanical activity. Stutz and others[131] also indicate that Cedilanid decreased and shortened the action current, an effect which could also be produced by water extraction. These investigators conclude that "the similarity between the effects of water extraction and that of Cedilanid is possibly the result of electrolyte changes which occur under both conditions" (p. 563), that is, a loss of potassium or of potassium and sodium.

G. *Toxic effects of digitalis.* As mentioned in the introduction, only those papers which contribute to an understanding of the action of digitalis will be included in this review.

In addition to the authors previously cited[88,89,90,105] Garb and Venturi[41] maintain that varying the potassium concentration over a wide range did not affect the inotropic response to ouabain, but in the higher concentrations, delayed or reduced the onset of arrhythmias produced by ouabain. They conclude that potassium concentration was of consequence only in producing digitalis toxicity.

Smith and others[128] find that the toxic effects of ouabain could be exaggerated by prostigmine and acetylcholine and decreased a trifle by atropine, but these drugs did not alter the increased oxygen consumption provoked by ouabain.

The relation of insulin to the toxicity of cardiac glycosides has been investigated. Keyl and Dragstedt[69], using the embryonic chick heart as test material, show that the toxicity of digitalis was increased by insulin and also by increasing the age of the embryo. Presumably the critical factor with regard to age was the development of a functional pancreas. Travis, Keyl and Dragstedt[134] find that normal dogs, and normal dogs made hyperglycemic with glucose, were more sensitive to k-strophanthin than depancreatectomized dogs. They believe that "insulin facilitates the transport of glycosides . . ." (p. 150).

III. Summarizing and Concluding Remarks

What is the fundamental action of digitalis?

In a review article such as this, it is not customary for the reviewer to draw any conclusions or to attempt a thumbnail-type summary, probably because it is assumed that the entire article is a concise summary from which every unnecessary word has been deleted by the author, his staff, or the ever-vigilant editors.

The present reviewer suffers no such qualms. His only deterrent is that a summary of this paper would have to take the form of a theory of the action of digitalis, a subject already suffering from a plethora of theories (see Kisch[73] for a unique theory that could not be fitted into any previous category).

Therefore, it may be assumed that the following points have been established by the efforts of almost countless scien-

tists.* First, energy from some metabolic source must be available if digitalis is to work. Second, the formation and breakdown of ATP must occur as required. Third, the components of muscular contraction must be intact and functional. Fourth, the "potassium-sodium pump" must be functional.

If these conditions exist, the stage is set for the action of digitalis. It is hypothesized, then, that digitalis exerts its effects in the following manner: First, it abets the loss of potassium from the cell that occurs normally during a muscular contraction. Second, the loss of potassium allows the formation of an actomyosin-ATP complex, as in normal muscular contraction; the actomyosin-ATP complex then catalytically releases energy which it harvests for its own contraction. The effect of digitalis in this step is nothing more than an exaggeration of the normal process of muscular contraction. Third, certain other effects of digitalis influence the extent of the contractile process: digitalis acts as an inhibitor of ATP-ase, thus preparing the cell for maximum contraction. And fourth, the toxic effects of digitalis may be regarded as a further exaggeration of the previous three steps, aggravated by the anticholinesterase activity of digitalis.

This theory may serve as a model or a working thesis for future efforts. Certainly it is not completely substantiated by undeniable facts. Many of the contentions put forth here must be repeated, verified, modified, corrected, or discarded. Many of the points upon which this theory depends, but which have not even been discussed (such as the method by which digitalis causes the loss of potassium) must be clarified.

Of course, a magnificent effort such as the attempt to prove any theory, has as its goal more than the acquisition of mere knowledge. It has in addition, the goal of a better understanding of the action of digitalis, and the hope that this drug will be used with ever-increasing success.

*See references 1 to 149, inclusive. The author acknowledes that his sole contribution to this theory is a sharp pencil, a bottle of ink, a thick stack of index cards, and a typewriter ribbon chronically in need of replacement.

REFERENCES

1. Aikawa, J. K., and E. L. Rhoades: Proc. Soc. Exper. Biol. Med., 9:*332*, 1955.
2. Alstrom, I.: Acta Med. Scand., 148:*439*, 1954; CA 48:*8953e*, 1954.
3. Baker, J. B. E.: Brit. J. Pharmacol., 2:*259*, 1947.
4. Banga, I., and G. Josepovits: Hung. Acta Physiol., 1:*67*, 1947; CA 42:*8833d*, 1948.
5. Barnes, J. M., J. I. Duff, and C. J. Threlfall: J. Physiol., 130:*585*, 1955
6. Barron, E. S. G.: Advances in Enzymology, 3:*149*, 1943.
7. Bertelli, A., and E. Mussini: Boll. soc. ital. biol. sper., 31:*1168*, 1955; CA 50:*10277b*, 1955.
8. Bianchi, C.: Arch. intern. pharmacodynamie, 92:*253*, 1953; CA 47:*11553e*, 1953.
9. Bine, R., Jr., M. Friedman, S. O. Byers, and C. Bland: Circulation, 4:*105*, 1951.
10. Bowen, W. J.: Am. J. Physiol., 165:*10*, 1951.
11. Bowen, W. J.: Fed. Proc., 11:*16*, 1952.
12. Bozler, E.: Experientia, 9:*1*, 1953.
13. Brody, T. M.: Pharmacol. Rev., 7:*635*, 1955.
14. Burdette, W. J. Jr., Lab. and Clin. Med., 40: *867*, 1952.
15. Burdette, W. J., Am. Heart J., 46:*602*, 1953.
16. Chatterjee, M. L.: Brit. J. Pharmacol., 9:*285*, 1954.
17. Chen, G., and E. M. K. Geiling: Schweiz. Med. Wochschr., p. 974, 1947.
18. Clark, A. J., and A. C. White: J. Physiol., 66:*185*, 1928.
19. Cleland, K. W., and E. C. Slater: Biochem. J., 53:*547*, 1953.
20. Conn, H. L., Jr.: Am. J. Physiol., 184:*548*, 1956.
21. Danielopolu, D.: Cardiologia, 12:*66*, 1947.
22. del Pozo, E. C., and E. G. Pardo: J. Pharm. Exper. Therap., 97:*144*, 1949.
23. Dubuisson, M.: *Muscular Contraction*, Charles C. Thomas, Springfield, Illinois, 1954.
24. Edman, K. A. P.: Acta Physiol. Scand., 21: *230*, 1950 CA 45:*3511i*, 1951.
25. Edman, K.A.P.: Experientia, 7:*71*, 1951.
26. Edman, K.A.P.: Acta Physiol. Scand., 30:*69*, 1953; CA 48:*4699c*, 1954.
27. Edman, K. A. P.: Experientia, 9:*107*, 1953.
28. Ellis, S.: J. Pharm. Exper. Therap., 105:*381*, 1952.
29. Ellis, S.: J. Pharm. Exper. Therap., 109:*233*, 1953.

*In order to bring to the interested reader the sense of those articles written in a difficult language or published in a journal that is sometimes hard to find, references in Chemical Abstracts (CA) are frequently included.

30. Engelhardt, W. A., and M. N. Ljubimowa: Nature, 144:*668*, 1939.
31. Engelhardt, W. A.: The enzymology of myosin. 2nd Congr. intern. biochem., Symposium cycle tricarboxylique, Paris, July 21, 1952: CA 47:*10565h*, 1953.
32. Erzina, G. A.: Doklady Akad. Nauk SSSR, 77:*753*, 1951; CA 45:*7247h*, 1951.
33. Finkelstein, M.: Fed. Proc., 7:*218*, 1948.
34. Finkelstein, M., and O. Bodansky: J. Pharm. Exper. Therap., 94:*274*, 1948.
35. Fischer, H., P. Huber and H. Langemann: Helv. Physiol. et Pharmacol. Acta, 9:*416*, 1951; CA 46:*3653c*, 1952.
36. Foa, P. P.: Personal communication.
37. Frey, J.: Arch. exper. Pathol. u. Pharmakol., 216:*473*, 1952; CA 47:*5014f*, 1953.
38. Friedman, M. and S. St. George: J. Clin. Invest., 32:*569*, 1953.
39. Fuhrman, G. J., F. A. Fuhrman, and J. Field, 2nd: Am. J. Physiol., 163:*642*, 1950.
40. Fulton, J. F.: A Textbook of Physiology, W. B. Saunders Co., Philadelphia, 1955.
41. Garb, S., and V. Venturi: J. Pharm. Exper. Therap., 112:*94*, 1954.
42. Gertler, M. M., J. Kream, J. W. Hylin, H. Robinson, and E. G. Neidle: Proc. Soc. Exp. Biol. Med., 92:*629*, 1956.
43. Glynn, I. M.: J. Physiol., 128:*56P*, 1955.
44. Goodman, L. S., and A. Gilman: The Pharmacological Basis of Therapeutics, The Macmillan Company, New York, 1955.
45. Greef, K.: Deut. med. Wochschr., 81:*666*, 1956 CA 50:*13287i*, 1956.
46. Greiner, T.: J. Pharm. Exper. Therap., 105: *178*, 1952.
47. Grisolia, S.: Biochim. et Biophys. Acta, 18: *437*, 1955; CA 50:*2869f*, 1956.
48. Guyton, A. C.: Textbook of Medical Physiolcgy, W. B. Saunders Co., Philadelphia, 1956.
49. Hajdu, S.: Am. J. Physiol. 174:*371*, 1953.
50. Hajdu, S. and A. Szent-Gyoryl: Am. J. Physiol., 168:*159*, 1952.
51. Hajdu, S., and A. Szent-Gyorgyi: Am. J. Physiol., 168:*171*, 1952.
52. Haltori, K.: Folia Pharmacol. Japan, 51:*254*, 1955: CA 50:*15919b*, 1956.
53. Harvey S. C., and G. R. Pieper: J. Pharm. Exper. Therap., 114:*14*, 1955.
54. Hayashi, T.: J. Gen. Physiol., 36:*139*, 1952.
55. Helmreich, E.: Biochem. Zeitschr., 321:*144*, 1950: CA 45:*2998e*, 1951.
56. Helmreich, E. and H. Nowy: Arch. Exper. Path. Pharmakol., 213:*411*, 1951; CA 46: *11376f*, 1952.
57. Helmreich, E., and K. Simon: Z. Naturforsch., 7b:*341*, 1952; CA 47:*2380c*, 1953.
58. Herrmann, R. G., G. E. Flamboe and K. K. Chen: J. Pharm. Exper. Therap., 112:*23*, 1954.
59. Hermann, R. G.: Arch. intern. pharmacodynamie, 81:*235*, 1950; CA 44:*7428d*, 1950.
60. Hermann, V. Sz., and G. Josepovits: Nature: 164:*845*, 1949.
61. Hisada, S. and T. Nakashima: Nagoya Med. J., 1:*277*, 1953; CA 48:*6597c*, 1954.
62. Holland, W. C., and C. E. Dunn: Am. J. Physiol., 179:*486*, 1954.
63. Holland, W. C., M. E. Greig, and C. E. Dunn: Am. J. Physiol., 176:*227*, 1954.
64. Horvath, I., E. Kiraly, and J. Szerb: Nature, 164:*792*, 1949.
65. Hunter, F. E. Jr.: Proc. 3rd Intern. Congr. Biochem., Brussels, 1955:*298;* CA 50:*14831c*, 1956.
66. Hunziker, H.: Vierteljarischr. naturforsch. Ges. Zurich, 99:*263*, 1954; CA 49:*5663h*, 1955.
67. Johnson, J. A.: Am. J. Physiol., 187:*328*, 1956.
68. Kahn, J. B., Jr., G. H. Acheson, and S. B. Cohen: J. Pharm. Exper. Therap., 115:*305*, 1955.
69. Keyl, A. C., and C. A. Dragstedt: J. Pharm. Exper. Therap., 112:*129*, 1954.
70. Kimura, T. E.: Proc. Soc. Exper. Biol. Med., 69:*419*, 1948.
71. Kimura, T. E.: Arch. Intern. Pharmacodynamie, 79:*306*, 1949; CA 43:*7131h*, 1949.
72. Kimura, T. T., and K. P. DuBois: Science, 106:*370*, 1947.
73. Kisch, B.: Exp. Med. and Surg., 4:*4*, 1946.
74. Konzett, H., and E. Rothlin: Helv. Physiol. Pharmacol. Acta, 8:*C64*, 1950; CA 45:*3504c*. 1951.
75. Konzett, H., and E. Rothlin: Arch. Intern. pharmacodynamie, 89:*343*, 1952; CA 46: *9193a*, 1952.
76. Krebs, H. A.: Advances in Enzymology, 3:*191*, 1943.
77. Kutschera-Aichberger, H.: Wein, klin. Wochschr., 67:*675*, 1955; CA 50:*2855f*, 1956.
78. Lamprecht, W.: Deut. med. Wochschr., 81: *534*, 1956; CA 50:*10270g*, 1956.
79. Lange, G.: Biochem. Zeitschr., 326:*172*, 1955; CA 50:*10143i*, 1956.
80. Langemann, H., T. M. Brody, and J. A. Bain: J. Pharm. Exper. Therap., 108:*274*, 1953.
81. Lee, K. S.: J. Pharm. Exper. Therap., 109: *304*, 1953.
82. Lee, K. S.: J. Pharm. Exper. Therap., 109: *313*, 1953.
83. Lee, K. S.: J. Pharm. Exper. Therap., 112: *484*, 1954.
84. Lehninger, A. L.: The Harvey Lectures, 49:*176*, 1953-1954.
85. Levinson, L., and M. Aisner: Am. J. Med., 6:*510*, 1949.
86. Lichtneckert, I., and F. B. Straub: Hung. Acta Physiol., 2:*50*, 1949; CA 45:*8644c*, 1951.
87. Lorber, V.: Circulation Research, 1:*298*, 1953.
88. Lown, B., H. Salzberg, C. D. Enselberg, and R. E. Weston: Proc. Soc. Exper. Biol. Med., 76:*797*, 1951.
89. Lown, B., J. M. Weller, N. Wyatt, R. Hoigne, and J. P. Merrill: J. Clin. Invest., 31:*648*, 1952.
90. Lown, B., N. F. Wyatt, A. T. Crocker, W. T. Goodale and S. A. Levine: Am. Heart J., 45:*589*, 1953.
91. Luisada, A. A., and M. Weiss: Am. J. Physiol., 176:*123*, 1954.
92. Lundin, G., and G. Strom: Acta Physiol. Scand., 15:*279*, 1948; CA 42:*8342a*, 1948.
93. Mallov, S., and J. S. Robb: Fed. Proc., 8:*104*, 1949.

94. Manery, J. F., D. R. H. Gourley, and K. C. Fisher: Can. J. Biochem. and Physiol., 34:*393*, 1956; CA 50:*17097c*, 1956.
95. Matsuoka, D. T., and P. R. Saunders: Proc. Soc. Exper. Biol. Med., 74:*879*, 1950.
96. Meier, R., and J. Tripod: Arch. Intern. pharmacodynamie, 89:*326*, 1952; CA 46: *9192i*, 1952.
97. Mommaerts, W. F. H. M.: Am. J. Physiol., 182:*585*, 1955.
98. Mommaerts, W. F. H. M., and J. C. Rupp: Nature, 168:*957*, 1951.
99. Munchinger, R.: Cardiologia, 22:*145*, 1953.
100. Nagayama, S.: Nisshin. Igaku, 43:*10*, 1956; CA 50:*7922a*, 1956.
101. Needham, D. M.: Biochim. et Biophys. Acta, 4:*42*, 1950.
102. Niedergerke, R.: J. Physiol., 134:*569*, 1956.
103. Nowy, H., and E. Helmreich: Arch. Exper. Path. Pharmakol., 213:*402*, 1951.
104. Okita, G. T., P. J. Talso, J. H. Curry, Jr., F. D. Smith, Jr., E. M. K. Geiling: J. Pharm. Exper. Therap., 115:*371*, 1955.
105. Page, E., and J. D. Real: Circulation Research, 3:*501*, 1955.
106. Pardo, E. G., D. Barcia-Tellez, and E. C. del Pozo: Pharm. Exper. Therap., 101:*63*, 1951.
107. Porro, A.: Arch. sci. biol. (Italy), 39:*416*, 1955; CA 50:*14110d*, 1956.
108. Proctor, C. D., J. Rebar, Jr. and B. Tigerman: Ann. N. Y. Acad. Sco., 62:*377*, 1955.
109. Proctor, C. D., J. Rebar, Jr., and B. T. Rebar: Fed. Proc., 15:*470*, 1956.
110. Ransom, V. R., and T. A. Loomis: J. Pharm. Exper. Therap., 104:*219*, 1952.
111. Read, W. O., and F. E. Kelsey: Science, 125:*120*, 1957.
112. Rebar, J., Jr., B. T. Rebar, and C. D. Proctor: In press.
113. Reiter, M.: Arch. Exper. Pathol. Pharmakol., 219:*315*, 1953; CA 47:*10726ab*, 1953.
114. Reiter, M., and E. S. G. Barron: Arch. Exper. Pathol. Pharmakol., 214:*341*, 1952; CA 46:*8271i*, 1952.
115. Ringer, S.: J. Physiol., 3:*380*, 1880-1882; J. Physiol., 4:*29*, 1883; J. Physiol., 4:222, 1883.
116. Robb, J. S., and S. Mallov: J. Pharm. Exper. Therap., 108:*251*, 1953.
117. Rothlin, E., and O. Schoelly: Helv. Physiol. et Pharmacol. Acta, 8C:*69*, 1950; CA 45: *4825c*, 1951.
118. Rothlin, E., M. Taeschler, and A. Cerletti: Circulation Research, 3:*32*, 1955.
119. Salter, W. T., I. J. Sciarini, and J. Gemmel: J. Pharm. Exper. Therap., 96:*372*, 1949.
120. Schatzmann, H. J.: Helv. Physiol. Acta, 11:*346*, 1953.
121. Schatzmann, H. J., and P. N. Witt: J. Pharm. Exper. Therap., 112:*501*, 1954.
122. Schreiber, S. S.: Am. J. Physiol., 185:*337*, 1956.
123. Segre, G.: Arch. Intern. Pharmacodynamie, 75:*227*, 1948; CA 42:*8953i*, 1948.
124. Segre, G.: Arch. Intern. Pharmacodynamie, 80:*336*, 1949; CA 44:*3607i*, 1950.
125. Segre, G.: Boll. soc. ital. biol. sper., 26:*939*, 1950; CA 47:*6450i*, 1953.
126. Shinohara, M.: Folia Pharmacol. Japan, 51:*623*, 1955; Brevaria 31 (in English); CA 50:*17166d*, 1956.
127. Smith, J. A., and M. Post: Am. J. Physiol., 163:*751*, 1950.
128. Smith, J. A., M. Glassman, A. H. Lind, M. Post, H. Sohn, and S. Warren: Proc. Soc. Exper. Biol. Med., 86:*747*, 1954.
129. Snellman, O., and B. Gelotte: Nature, 165: *604*, 1950.
130. St. George, S., M. Friedman, and T. Ishida: Proc. Soc. Exper. Biol. Med., 83:*318*, 1953.
131. Stutz, H., E. Feigelsen, J. Emerson, and R. J. Bing: Circulation Research, 2:*555*, 1954.
132. Szent-Gyorgyi, A.: Chemistry of Muscular Contracttion, Academic Press, Inc., New York, 1951.
133. Szent-Gyorgyi, A.: Chemical Physiology of Contraction in Body and Heart Muscle, Academic Press, Inc., New York, 1953.
134. Travis, J. W., A. C. Keyl, and C. A. Dragstedt: J. Pharm. exper. Therap., 117:*148*, 1956.
135. Weber, H. H.: Biochim. et Biophys. Acta, 12:*150*, 1953.
136. Weber, H. H.: The Harvey Lectures, 49:37, 1953.
137. Whitehorn, W. V.: Proc. Soc. Exper. Biol. Med., 85:*268*, 1954.
138. Wilbrandt, W.: Schweiz. med. Wochschr., 85:*315*, 1955; CA 49: *11168i*, 1955.
139. Wilbrandt, W., and R. Caviezel: Helv. Physiol. et Pharmacol. Acta, 12:C*40*, 1954; CA 48:*13069c*, 1954.
140. Witt, P. N., and H. J. Schatzmann: Helv. Physiol. et Pharmacol. Acta, 12:C*44*, 1954; CA 48:*13069c*, 1954.
141. Wollenberger, A.: J. Pharm. Exper. Therap., 91:*39*, 1947.
142. Wollenberger, A.: Am. J. Physiol., 150:*733*, 1947.
143. Wollenberger, A.: J. Pharm. Exper. Therap., 97 (part 2):*311*, 1949; Pharm. Rev., 1:*311*, 1949.
144. Wollenberger, A.: Fed. Proc., 8:*348*, 1949.
145. Wollenberger, A.: J. Pharm. Exper. Therap., 103:*123*, 1951.
146. Wollenberger, A.: Arch. Exper. Pathol. u. Pharmakol., 219:*408*, 1953; CA 47:*11542h*, 1953.
147. Wollenberger, A., and M. L. Karsh: J. Pharm. Exper. Therap., 105:*477*, 1952.
148. Wollenberger, A., and B. Wahler: Arch. Exper. Pathol. u. Pharmakol., 228:*134*, 1956; CA 50:*8899e*, 1956.
149. Woodbury, L. A., and H. H. Hecht: Circulatiton, 6:*172*, 1952.

PHYSIOLOGIC MEDIATION OF PSYCHIC STIMULI IN DIABETES MELLITUS *

PIERO P. FOA, M.D., Ph.D.**

The maintenance of normal somatic and psychologic functions requires the reception and integration of sensory stimuli, their intellectual and emotional evaluation and their transformation into movement or secretory activity. Thus the "mind" becomes an integral part of homeostasis and plays an important role in the pathogenesis of disease. The nature of these psychosomatic relationships is becoming more clear as a result of varied and intensive investigations, some of which date as early as the seventeenth century, when Thomas Willis, describing the sweet taste of diabetic urine, said that the disease was due to "prolonged sorrow."

One type of investigation is concerned with the study of personality patterns in diabetes. According to Dunbar[1], for instance, the diabetic patient suffers from a conflict between hatred and submission to parental figures and from inadequate sexual adjustment. This interesting hypothesis, illustrated by selected case histories, is based on "proof by examples" which cannot be considered conclusive and could not be confirmed by a recent study of Kubany, Danowski and Moses[2]. These authors, although recognizing that "diabetes mellitus produces many psychologic problems which may result in abnormal behavior . . ."[3], were unable to find any intelligence or personality pattern characteristic of the diabetic patient.

Anxiety, fear and other psychologic problems, due to the awareness of chronic disease, not only may create obstacles in the path of therapy and indirectly affect the disease itself[4,5], but may influence its basic pathogenesis, resulting in a mutual interplay of disease and emotional state which has been called the "psychobiologic constellation"[6]. Hinkle and Wolf[7] studied the marked effects of experimentally induced emotional trauma and of stressful life situations on the course of diabetes. These authors observed that a metabolic pattern characterized by decreased carbohydrate tolerance and ketosis, occurs in prolonged fasting and suggest the interesting hypothesis that diabetes mellitus may be the result of inappropriate adaptive mechanisms to symbolic starvation, such as real or imaginary loss of affection and emotional support or threats to the patient's security. A striking example of the relationship of anxiety to diabetes is that of a patient suffering from repeated episodes of emotionally induced diabetic coma.

Another line of investigation, based on the classic observations of Pavlov, Cannon and Selye, is concerned with the anatomic and physiologic links which translate psychologic stimuli into somatic effects.

This review will summarize briefly some of the most recent contributions to this aspect of the problem and discuss the thesis that diabetes mellitus is, at least in part, a disorder of adaptation to emotional or physical stimuli, possibly originating in the neocortex or carried to the neocortex by afferent pathways. According to this hypothesis these stimuli would descend from the neocortex to the philogenetically older limbic system and from this to the hypothalamus, the pituitary and other effector organs via nervous or humoral transmission. Thus fright, emotional upheavals, distressing memories, or physical insults, would cause autonomic responses (pallor, blushing, sweating, elevation of blood pressure, syncope, tachycardia, bronchial or intestinal spasm) or endocrine disturbances, such as changes in diuresis and ovulatory cycle, dysmenorrhea, hyperfunction of thyroid and adrenal cortex, increased secretion of epinephrine, hyperglycemia

* Aided by grant No. A-522 from the National Institute of Arthritis and Metabolic Diseases, N.I.H., Public Health Service.

** Professor of Physiology and Pharmacology, The Chicago Medical School.

and glycosuria. In turn, these autonomic and endocrine responses may be a source of anxiety[9] and of physical stress and a vicious cycle may become established.

The Nervous Pathways to the Hypothalamus and the Hypothalamo-Endocrine Interrelationships.

According to some investigators[10, 11] the major pathways through which environmental and psychic stimuli may reach the hypothalamus derive from: 1) the hippocampus, 2) the piriform lobe, 3) the cingular gyrus, anterior insular and orbito-frontal cortex, 4) the amygdala and 5) the globus pallidus.

The first four of these structures are part of the so-called limbic system[12] which, receiving neo-cortical afferents, may function as a bridge between neocortex and hypothalamus through which emotional stimuli may activate the endocrine system. In addition, the hypothalamus gives rise to hypothalamo-cortical pathways, providing the anatomical basis for reverberating circuits and feed-back mechanisms. From the hypothalamus stimuli may reach the periphery either through the autonomic nervous system or through the endocrine glands.

Evidence for direct effects of the central nervous system on the secretory activity of the islets of Langerhans and on the regulation of blood sugar levels has been discussed elsewhere[13, 14] and, although the function of the pancreatic innervation in the adjustment of blood sugar level appears to be an accessory and not a necessary one, the possibility that it may cause temporary changes in diabetes cannot be denied *a priori*. In contrast with this uncertain role of the nervous system in the regulation of the endocrine functions of the pancreas, emotional or somatic stimuli carried by the splanchnic nerves to the adrenal medulla cause an increase in secretory activity resulting in hyperglycemia and, sometimes, glycosuria[15]. The great sensitivity of this mechanism is indicated by the recent observation that the relatively minor stress of awakening from a normal sleep may cause a 40% increase in the adrenalin concentration of venous blood[16]. In addition to the pancreas and the adrenal medulla, the hypothalamus sends stimuli to the anterior pituitary. Recent investigations indicate that normal pathways between hypothalamus and pituitary seem to be required for a regulated secretion of thyroid stimulating hormone (TSH) and for a normal TSH response to cold and anesthesia[17]. In addition there is evidence of the existence of a hypothalamic center or centers controlling thyroid growth and ACTH secretion[18, 19] The stimulation of ACTH secretion by physical or mental stress is a well known phenomenon and has been confirmed recently by studies of adrenal steroids in blood and urine[20, 24].

The function of the central nervous system in ACTH release is demonstrated also by the following observations: 1) venous blood from the brain of stressed hypophysectomixed rats causes eosinopenia in normal rats[25]; 2) mid-brain decerebration reduces the concentration of aldosterone and hydrocortisone in the adrenal blood[26]; 3) reserpine, a diencephalic tranquillizer[27] and injury to the supra-optico-hypophysial tract[28] inhibit stress-induced ACTH secretion and 4) stimulation of the anterior hypothalamus in man causes an increased output of adrenal steroids[29].

There seems to be little doubt that the hypothalamus is largely responsible for regulating the secretion of follicle stimulating hormone (FSH) and luteotrophic hormone (LH) which may explain the effects of courtship, sex display and other environmental, sensory and psychic factors on ovulation, the menstrual cycle and on the activity of the reproductive organs in general[10,30,31]. The mechanism of this hypothalamic control of the anterior lobe of the pituitary has not been elucidated completely, though most investigators believe that it depends upon a humoral mediator reaching the gland via its portal vessels[31].

This hypothesis is based on the following evidence: 1) section of the pituitary stalk causes a reduction in FSH, ACTH and TSH secretion, if the regeneration of the portal vessels is effectively pre-

vented; 2) anterior pituitary glands, transplanted to a site where they become revascularized by portal vessels, show normal activity; 3) anterior pituitary glands transplanted elsewhere grow, but function at a reduced rate; 4) tissue cultures of anterior pituitary cease to produce ACTH after 4 days of incubation, but resumes its production if fragments of hypothalamic tissue or hypothalamic extracts are added[32]. The nature of the hypothalamo-hypophyseal humoral mediator is debated; some investigators[33,34] suggest that it might be identical to the posterior pituitary hormones secreted under a number of nervous and emotional stimuli[35], by the cells of the supraoptic and paraventricular nuclei[36], while other investigators[32] believe that the hypothalamus secretes a specific neurohumoral transmitter (or transmitters).

Evidence that the hypothalamus may contain centers regulating food consumption and body weight is also available[37] and is of interest in view of the relationship between diabetes and obesity.

Effects of the Anterior Pituitary and its Target Glands on Diabetes.

The classic experiments of Houssay and others have demonstrated that hypophysectomy leads to "amelioration" of pancreatic diabetes, while the administration of anterior pituitary extracts (APE) causes impairment of glucose tolerance, increased insulin resistence and, sometimes, ketosis*. This disturbance may be either temporary (idiohypophysial diabetes) or permanent (metahypophysial diabetes).

Pituitary diabetes in the normal animal or aggravation of existing diabetes in the alloxanized animal can be obtained also with purified pituitary hormones, such as growth hormone (somatotrophic hormone or STH), adrenocorticotrophic hormone (ACTH) and prolactin. The mechanism of action of these hormones has been discussed extensively elsewhere[38] and is not fully understood. STH may cause hyperglycemia by injuring the insulin-secreting β cells of the islets of Langerhans, by stimulating glucagon secretion or by bringing about an insulin-reversible inhibition of glucose utilization. ACTH and the adrenal cortical hormones (ACH) may enhance the effects of STH and glucagon or inhibit glucose uptake by the tissues directly. In any case, chronic hyperglycemia would result, leading to increased insulin demand, to excessive stimulation of the islets of Langerhans and to their final exhaustion. In addition, ACTH and ACH may cause a decrease in the supply of SH— groups available for the synthesis of insulin and necessary for the activity of several enzymes of carbohydrate metabolism.

Prolactin may have an action similar to that of STH and ACTH and the sequence of decreased pancretic reserve, increased insulin demand, stimulation and exhaustion of the B cells may apply to this hormone also. A possible role of the gonadotrophins in diabetes is suggested by the observation that androgens increase the incidence and severity of diabetes in rats, that certain derivatives of progesterone also have a diabetogenic effect, and that the administration of estrogens at first causes hyperglycemia and glycosuria followed, with prolonged treatment, by improvement of the diabetic syndrome.

In addition to the vicious cycle of hyperglycemia, increased insulin demand, pancreatic stimulation, pancreatic exhaustion and hyperglycemia, other effects may be set in motion by an excessive stimulation of the anterior pituitary. For instance STH and ACTH may stimulate the formation of ketone bodies by the liver[39], ketosis may stimulate the secretion of ACH[40] and these, in turn, may aggravate the syndrome and, possibly, contribute to some of its complications[41]. Diabetes may also be influenced by epinephrine which, one the one hand, causes hyperglycemia by stimulating liver glycogenolysis and, on the other hand, stimulates the secretion of ACTH and adrenal cortical hormones[42].

The hormones of the posterior pituitary also cause hyperglycemia, but only in very large doses. However it is pos-

* For an extensive bibliography the reader is referred to two recent reviews (13, 38).

sible that, when dehydration due to excessive glycosuria and ketonuria stimulates the hypothalamic osmoreceptors, the excessive production of antidiuretic hormone may stimulate the anterior pituitary and further aggravate the situation.

Conclusions.

The hypothalamus appears to mediate the somatic manifestations of emotion, not only by regulating autonomic reactions such as pallor, blushing tachycardia, rise in blood pressure, sweating, tremors and increased smooth muscle activity, but also by activating the endocrine system. In the case of diabetes mellitus these concepts may be summarized by the following diagram:

In this manner anxiety and other psychodynamic forces may cause somatic changes and precipitate or aggravate acute or chronic illness, the awareness of which, in turn, may become a source of anxiety. The participation of the hypothalamo-hypophysial system, capable of regulating a multitude of functions, may explain the great variety of organic and functional changes which can be precipitated by psychogenic stimuli and offers hope for a better understanding not only of the relationships between psycho-endocrine and other psychosomatic phenomena but of psychologic processes in general.

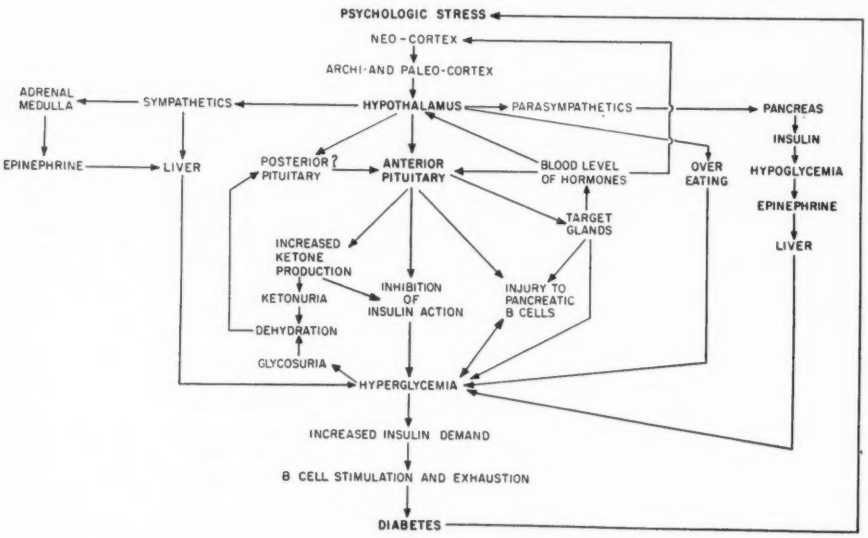


Figure 1

IV. BIBLIOGRAPHY

1. Dunbar, F., Emotions and Bodily Changes, Columbia Univ. Press, New York, 1954.
2. Kubany, A. J., Danowski, T. S., and Moses, C., Diabetes, *5:* 462, 1956.
3. Fischer, A. E., and Dolger, H., Arch. Int. Med., *78:* 711, 1946.
4. Levinson, W., Flicker, D. J., Mayne, M. G., and Skwirsky, J., J. Newark Beth Israel Hosp., *5:* 3, 1954.
5. Marble, A., Duncan, G. G., Jackson, R. L., Guest, G. M., and Sheridan, E. P., Diabetes, *5:* 475, 1956.
6. Benedek, T., Psychosom. Med., *10:* 284, 1928.
7. Hinkle, L. E., Jr., and Wolf, S., J. Mt. Sinai Hosp., *19:* 537, 1952.
8. Peck, F. B., Sr., and Peck, F. B., Jr., Diabetes, *5:* 44, 1956.
9. Glaser, G. H., Psychosom. Med., *15:* 280, 1953 and *17:* 336, 1955.
10. Green, J. D., in Fields, W. S., Guillemin, R., and Carton, C. A., Hypothalamic-Hypophysical Interrelationships. C. C. Thomas, Springfield, 1956, p. 3.
11. Gloor, P., ibid., p. 74.

12. MacLean, P. D., in Wittkower, E., and Gleghorn, R., Recent Developments in Psychosomatic Medicine. Pitman, London, 1954 and Psychosom. Med., *17:* 355, 1955.
13. Foa, P. P., Ciba Foundation Coll. Endocrinol., *9:* 55, 1956.
14. Anderson, E., Bates, R. W., Hawthorne, E., Haymaker, W., Rioch, D. McK., Spence, W. T., and Wilson, H., Recent Progress Hormone Res., in press.
15. Cannon, W. B., Bodily Changes in Pain, Hunger, Fear and Rage, D. Appleton Co., New York, 1915.
16. Renton, G. H., and Weil-Malherbe, H., J. Physiol., *131:* 170, 1956.
17. Euler, v. C., and Holmgren, B., J. Physiol., *131:* 125, 137, 1956.
18. Greer, M. A., J. Clin. Endocrinol., *12:* 1259, 1952.
19. Greer, M. A., and Erwin, H. L., Endocrinol., *58:* 665, 1956.
20. Thorn, G. W., Jenkins, D., and Laidlaw, J., Recent Progress Hormone Res., *8:* 171, 1953.
21. Hume, D. M., Ciba Foundation Coll. Endocrinol., *4:* 87, 102, and Ann. Surg., *138:* 548, 1953.
22. Gleghorn, R. A., Psychosom. Med., *17:* 367, 1955.
23. Brodish, A., and Long, C. N. H., Endocrinol., *59:* 666, 1956.
24. Richards, J. B., and Pruitt, R. L., Endocrinol., *60:* 99, 1957.
25. Schapiro, S., Marmorston, J., and Sobel, H., Proc. Soc. Exp. Biol. Med., *91:* 382, 1956.
26. Rauschkolb, E. W., and Farrell, G. L., Endocrinol., *59:* 526, 1956.
27. Wells, H., Briggs, F. N., and Munson, P. L., Endocrinol., *59:* 571, 1956.
28. McCann, S. M., and Sydnor, K. L., Proc. Soc. Exp. Biol. Med., *87:* 369, 1956.
29. Pool, J. L., Clark, W. K., Hudson, P., and Lombardo, M., in Fields, W. S., Guillemin, R., and Carton, C. A., Hypothalamic-Hypophysical Interrelationships. C. C. Thomas, Springfield, 1956, p. 114.
30. Roizin, L., Rass. Neurol. Veget., *1:* 338, 1938.
31. Harris, G. W., in Fields, W. S., Guillemin, R., and Carton, C. A., Hypothalamic-Hypophysial Interrelationship. C. C. Thomas, Springfield, 1956, p. 31.
32. Guillemin, R., ibid, p. 46.
33. Stein, M., and Mirsky, I. A., ibid., p. 58.
34. Martini, L., and Rovati, V., Arch. intern. Pharmacodyn. Ther., *104:* 365, 1956.
35. Streeten, D. H. P., Univ. Mich. Med. Bull., *20:* 161, 1954.
36. Hild, W., in Field, W. S., Guillemin, R., and Cartin, C. A., Hypothalamic-Hypophysial Interrelationships. C. C. Thomas, Springfield, 1956, p. 17.
37. Mayer, J., French, R. G., Zighera, C. F., and Barrnett, R. J., Amer. J. Physiol., *182:* 75, 1955.
38. Foa, P. P., The Chicago Medical School Quart., *16:* 108, 1955.
39. Posberg Petersen, V., and Lotspeich, W. D., Am. J. Physiol., *182:* 273, 1955.
40. Anderson, E. A., Cutshall, B., Jr., and Pote, W. W., Jr., Clin. Res. Proc., *5:* 70, 1957.
41. Maengwyn-Davies, G. D., Lerman, S., Pogell, B. M., Stone, H. H., and Friedenwald, J. S., Bull. Johns Hopkins Hosp., *99:* 16, 1956.
42. Miller, R. A., and Dockrell, A. W., Endocrin., *58:* 550, 1956.

ELECTROMYOGRAPHIC STUDIES OF HUMAN RESPIRATION

JOHN E. PAULY, Ph.D.*

INTRODUCTION

Since the time of the ancients, anatomists and physiologists have attempted to determine the exact functions of the muscles of the human body. For the most part, their opinions were based upon observations of the muscles in the cadaver. Such a morphological analysis is quite adequate for certain muscles. For example, the brachialis originates on the anterior surface and intermuscular septa of the humerus and passes across the elbow joint to insert on the tuberosity and coronoid process of the ulna. Since the joint between the humerus and ulna moves in one plane only, it is an obvious and justifiable conclusion that the muscle flexes the forearm. But the action or function of other muscles such as the biceps brachii which has more complex attachments and passes over a joint that is capable of movement in more than one plane, are more difficult to analize. So a second technique was employed. The muscle being studied was palpated through the skin, and contractions felt by the observer were correlated with various body movements. Denervation, atrophy and surgical removal of muscles in both man and experimental animals and the resulting loss of function also have contributed to our understanding of muscle function and activity.

Most body movements are accomplished by two or more muscles acting synergistically. An analysis of a movement involving several muscles requires an understanding of all of the muscles involved as well as the relative contributions each makes to accomplish the action. Recent advances in the field of electronics have suggested a new research tool, the electromyograph. This instrument will record action potentials that invariably accompany muscle contraction and thereby objectively indicate the relative amount of activity of a muscle at any given time.

*Instructor, Department of Anatomy, The Chicago Medical School.

Early Investigations

The mechanics of respiration always has been a subject of interest to both the basic scientist and the clinician. Prior to the time of Galen, investigators of this problem believed that the diaphragm was the only muscle of inspiration. They held it was responsible for both the lateral and superior excursion of the rib cage. By assuming that the abdominal viscera would hold the dome of the diaphragm in place, it followed that diaphragmatic contraction would elevate the lower ribs and thereby lift the thoracic cage from below. Although willing to accept the diaphragm as the elevator of the lower ribs, Galen believed that the internal intercostal muscles assisted in inspiration and that the external intercostals acted in expiration. Thus the idea was suggested that more than one muscle was responsible for respiration and that muscles acted synergistically to increase and decrease the thoracic diameters. Vesalius believed that both intercostal muscles contracted at the same time and that the diaphragm was depressed and relaxed during inspiration thereby permitting the lower ribs to spread. He reasoned that activation of the diaphragm would cause a constriction of the lower ribs. Thomas Willis of Oxford in 1673 stated that the external intercostals are used for inspiration and the internal intercostals are used for expiration. Hamberger devised his famous model in 1747 and proposed the theory that the intercostal muscles widen and narrow the intercostal spaces. In 1833 Magendie suggested that the resistance of the viscera under the vault of the diaphragm was sufficient to increase the transverse diameter of the upper abdomen and spread the ribs outward during diaphragmatic contraction.

It is obvious that these early opinions were based on morphological observations and, for the most part, were not confirmed by experiments or direct observations in the living.

By the later part of the 19th century, the big question was whether the intercostal muscles were inspiratory or expiratory in function. In 1879, Martin and Hartwell[1] stated that it was impossible to determine their function by simple mechanical studies because (1) of the irregular shape of the ribs, (2) cutting any or all of the other muscles away in order to watch rib movements was not reasonable, because one could not know if the cut muscles hold the upper or the lower rib and therefore could not determine whether the intercostal muscle elevates the lower rib in inspiration or depresses the upper rib in expiration and (3) electrical stimulation of all respiratory muscles in their proper order and degree is impossible. So they devised an experiment that they were convinced would end the controversy. After etherizing cats and dogs and performing a tracheotomy, they made one longitudinal incision along the linea alba and a second transverse incision to expose the diaphragm. They removed the skin, serratus anterior, pectoralis major and minor and "other muscles" unilaterally in order to expose the 4th to the 10th external intercostal muscles. Then they cut the 8th and 9th costal cartilages medially, and the same ribs laterally, removed the 7th and 9th intercostal muscles and the external intercostal muscles only from the 8th interspace and dissected free the 7th intercostal nerve back to the spine. A tambour was fixed to the diaphragm and one rib segment was clamped. Strings from the other rib segment and from the tambour were connected to levers on a kymograph. The animal was "kept alive" by artificial respiration. The authors report that up to 15 contractions of the 8th internal intercostal segment occurred before lack of blood and exposure had its effect. They concluded that they had shown decisively the internal intercostal muscle to be expiratory in function. It is questionable whether their "preparation" could be considered a "normal state." It can be seen by the most casual observer that the transition from the morphological to the experimental type of analysis did not solve all of the problems confronting the physiologist immediately.

The diaphragm is without doubt the most important muscle of respiration. Paralysis of this muscle is attended by a loss of more than 50 percent of an individual's vital capacity. In a series of papers on the mechanics of respiration, Hoover[2 3 4], a Cleveland physician, stated that contraction of the diaphragm acts antagonistically to the scalenes and intercostals. Phrenic contraction increases the longitudinal diameter of the thorax and tends to narrow the subcostal angle and retract the lower end of the sternum. On the other hand, the scalenes and intercostals tend to enlarge the transverse and anterio-posterior diameters of the base of the thorax and lessen the longitudinal diameter. In the patient whose diaphragm is paralyzed from anterior poliomyelitis but whose scalenes and intercostal muscles are intact, Hoover noted an exaggerated inspiratory widening of the subcostal angle and flaring of the hypochondria, because the paralyzed diaphragm is incapable of exerting any restraint on its sterno-costal attachments. On the other hand, the patient with paralyzed intercostal muscles but with a normal diaghragm will have a retraction of the subcostal angle and sternum at each inspiration. Clinically, paralysis of the diaphragm and/or paralysis of the intercostal muscles is not encountered frequently. There are other conditions, however, which will give the same signs. In short, variations in respiratory movements of the sternum, subcostal angle and costal borders depend upon the higher or lower positions of the diaphragm. By clinical and experimental examples, Hoover showed that when the diaphragm was pushed upward it was placed at a mechanical disadvantage in approximating the points of origin and insertion of its muscle; but when it is displaced downward, it has a mechanical advantage and is cable of pulling the costal borders toward the central tendon. This tendon is pulled caudally during inspiration. When the dome is decreased by displacing it downward, contraction of the muscle pulls the origins toward the tendonous insertion. In emphysema, the enlarged

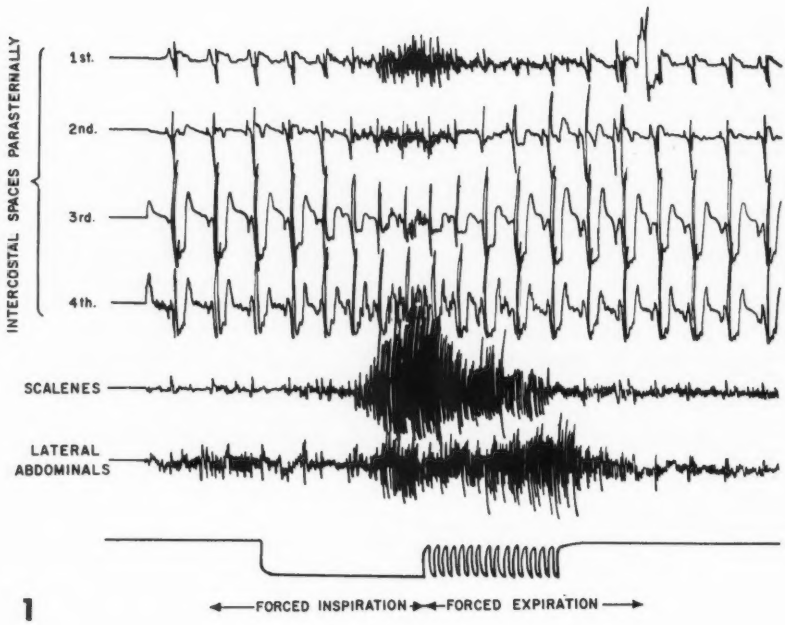


Figure 1

lungs fill the pleural sinuses bringing about a flattening of the diaphragm. Thus placed at a mechanical advantage, the diaphragm causes an inspiratory narrowing of the subcostal angle. An enlarged heart and pleurisy with effusion are only two of the many other conditions which may bring about this flattening.

In 1922, Hoover discovered that paralysis of all intercostal muscles would result in a loss of from 15 to 20 percent of vital capacity. The major disability incurred was associated with any effort that demands compression or distension of the lung against resistance. He suggested that these muscles are concerned wholly with rotation of the ribs laterally, superiorly and inferiorly and have nothing to do with the breadth of the intercostal spaces. Hoover disagreed with those physiologists who had assigned to these muscles the role of fixation of the sides of the thorax in order to furnish rigidity to the intercostal spaces. He believed that the parietal pleura amply serves this purpose.

Recent Investigations

A series of reports on instrumentation and muscle physiology from the late 19th century to the early 1930s included such important contributions as Braun's discovery of the cathode-ray tube in 1897, the analysis of action potentials by Piper in 1912 and the discovery of the motor unit potential and the coaxial needle electrode by Adrian and Bronk in 1929. These workers set the stage for modern studies of muscles.

Bronk and Ferguson[5] in 1935 dissected out the nerves to the external and internal intercostal muscles of a cat and claimed to record the discharge of impulses from single motor nerve cells. They reported rhythmic groups of impulses in the fibers to the external intercostal muscles and the interchondral part of the internal intercostal muscles during inspiration and in the fibers to the internal intercostal muscles with expiration. After eliminating afferent impulses resulting from respiratory movements, they still recorded rhythmic discharge of

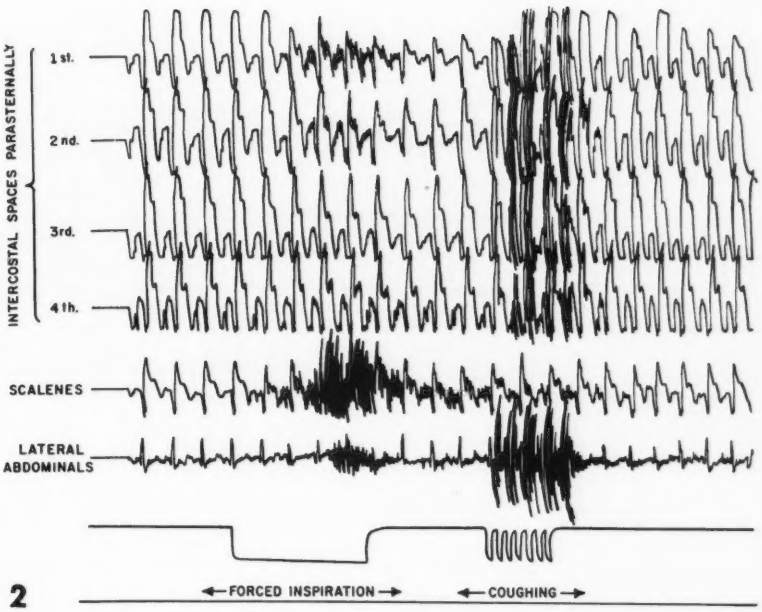


Figure 2

motor impulses from the nerves supplying the external and internal intercostal muscles. Virtually every standard textbook of physiology accepted these results; and many assumed that if such was the case in the cat, it must also be true for man.

Simultaneous electromyographic recordings from multiple locations on the human thorax with an electroencephalograph adapted for electromyography were made by Jones, Beargie and Pauly[6] in 1953. They reported a slight contraction of the scalenes during eupneic inspiration, marked activity in the scalenes, intercostals (Fig. 1), sternomastoid, and anterior edge of the trapezius during forced inspiration and a strong contraction of the abdominal wall muscles and intercostals in forced expiration and coughing (Fig. 2). They stated that the rectus abdominus, serratus anterior, pectoralis major and pectoralis minor take no part in eupneic or hyperpneic respiration. In 1957 Jones and Pauly[7] reported rhythmic activity from the intercostal muscles of a four year old boy during eupnea (Fig. 3) in the standing position and confirmed their previous findings of intercostal silence during

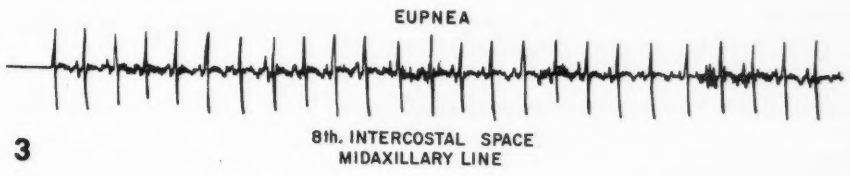


Figure 3

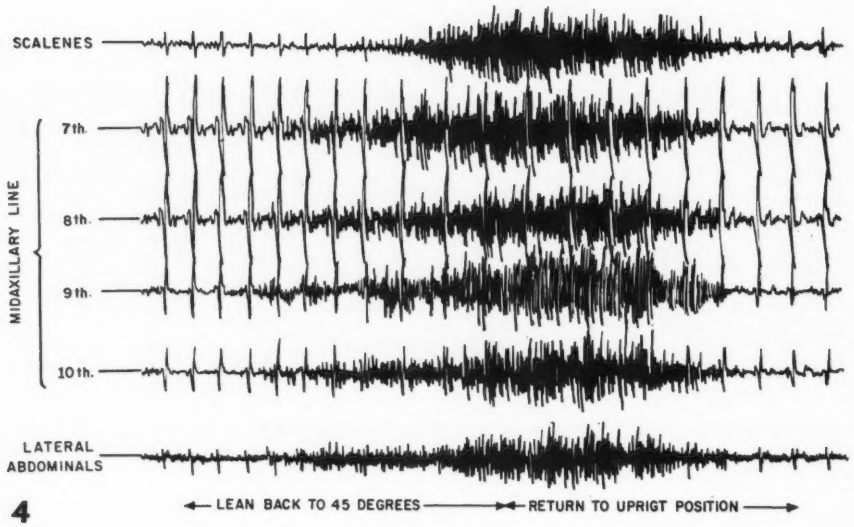


Figure 4

eupnea in the adult. They found that contractions of the intercostal muscles accompany various movements of the trunk (Figs. 4 and 5) and reasoned that perhaps these muscles are used in non-respiratory activity more than in ordinary breathing. Other investigators[8, 9] have reported isolated cases where intercostal activity has been recorded during quiet or slightly increased breathing.

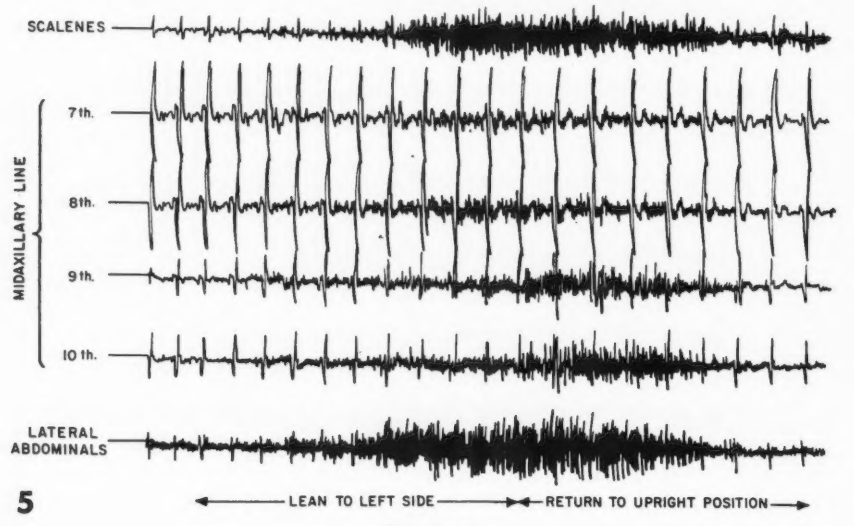


Figure 5

These findings are not constant in the adult and frequently can be altered by changes in posture.

In order to determine whether the internal and external intercostal muscles act together or independently in producing respiratory and trunk movements, Pauly, Jones, Jarach and Toman[10] employed a special assembly of four surface electrodes oriented in an intercostal space; and opposite electrode pairs led off to separate amplifiers feeding the x and y axes of a cathode ray oscilloscope (Fig. 6). It was possible to distinguish external and internal intercostal muscles from each other and from overlying muscles. They concluded that both intercostal muscles acted synergistically in performing the various movements.

TABLE I

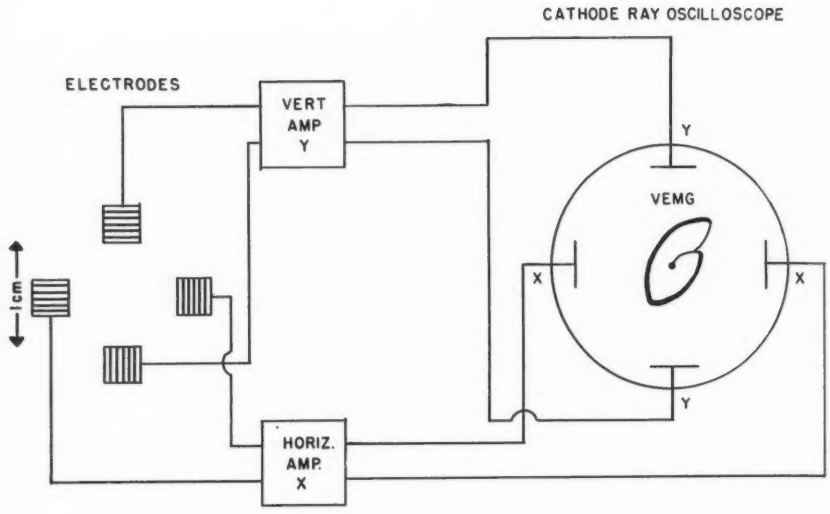
MUSCLES OF RESPIRATION

Muscles	Inspiration	Expiration
Diaphragm	1	0
Scalenes	2	0*
Intercostals		
External	3	2
Internal	3	2
" (Interchond.)	3	2
Sternomastoid	4	0*
Trapezius (Anter.)	4	0
Serratus Anter.	0	0
Pectoralis Major	0	0
Pectoralis Minor	0	0
Levatores Costarum	?	?
Serratus Poster. Super.	?	?
Errector Spinae	?	?
Levator Scapulae	?	?
Rhomboids	?	?
Quadratus Lumborum	?	?
Serratus Poster. Infer.	?	?
Latissimus Dorsi	0	0
Lateral Abdominal Mm.	0*	1
Rectus Abdominus	0	0

Discussion

Other factors influencing our breathing are the position of the body, posture and changes in intra-abdominal pressure. For example, if a person bends backward or to the side from a standing position, the intercostal muscles and the abdominal muscles unilaterally or bilaterally will tend to pull on the rib cage, thus limiting its excursion[7] (Figs. 4 and 5). Campbell and Green[11] using an air-filled, flaccid balloon and an electromanometer, recorded intra-abdominal pressure changes during quiet and forced ventilation. In eupnea, the pressure rose with inspiration and fell with expiration; but in hyperpnea, the pressure during expiration rose above that recorded at the end of inspiration. They called this change "reversal" and suggested that "it be regarded as a criterion of the participation of the abdominal muscles as an important expiratory force." It becomes fairly obvious that the abdominal muscles do not have a very significant role in expiration except at high levels of pulmonary ventilation.

All modern investigators are willing to admit that the diaphragm is the most important muscle of respiration. But the relative importance and influence of other muscles is still a subject of considerable dispute. In fact a respiratory role has been attributed to almost every muscle that inserts on, originates from, or crosses the thoracic cage. Table I lists those muscles commonly mentioned by physiologists and anatomists alike as being associated with breathing. Some of these muscles are almost impossible to study in the living human because of their great depth in the body; so question marks have been placed behind them in the table. There is no *electromyographic* evidence for their role in respiration. An *"O"* indicates no recordable activity, and the *numbers* refer to their position of importance. For example, the diaphragm is given the number *1*, because it is the most important muscle of inspiration; and the scalenes are given the number 2, because their importance in inspiration is exceeded only by the diaphragm. Electromyograms show an increase in activity of the scalenes during inspiration in eupnea[6]; while only in the exceptional case is any activity noted from the intercostals or abdominal muscles. In forced inpiration there is marked activity in the scalenes and the intercostal muscles[6, 7, 8, 9]. There is no difference in the activity of the muscles between the interosseous and intercartilagenous portions of the ribs, and a vectorelectromyographic analysis[10] confirms our suspicion that both the internal and external intercostal muscles contract simultaneously. In a maximal inspiratory effort, the sternomastoids[6, 12] and anterior



6 VECTORELECTROMYOGRAPHY (VEMG)

Figure 6

border of the trapezius also contract. Toward the end of this strong inspiratory effort, the lateral abdominal group also emits action potentials, probably as a result of a myotonic stretch reflex elicited by the pull on the abdominal wall as the thoracic excursion proceeds.

Expiration is usually a passive activity, probably due to the elastic recoil of the lungs and ribs as the diaphragm ascends. As breathing becomes more labored, however, the lateral abdominal muscles show short bursts of activity and act to pull the ribs down. In forced expiration, coughing and blowing into the tube of a mercury manometer (so as to force the column up to 50-150 mm. Hg. [Fig. 7]), the intercostal muscles become active[7], just as in force inspiration, the interosseous and interchondral portions become active simultaneously. It appears, therefore, that the concept expounded in the anatomical and physiological texts is untenable for the human, **i.e.** that the external intercostal muscles and interchondral part of the internal intercostals are active in inspiration, while the internal intercostal muscles are active in expiration.

Although medial rotation or flexion of the arm produced strong contractions from the pectoralis major, and action potentials were produced by the serratus anterior when the shoulder was protracted, these muscles did not show activity even in extreme forced inspiration[6].

Since vectorelectromyographic studies have not been made on the abdominal muscles, it is impossible to state definitely which ones are responsible for pulling the rib cage down. In our studies, the electrodes were always placed about an inch lateral to the lateral border of the rectus abdominus and an inch inferior to the subcostal border. It has been suggested that the rectus abdominus may act with the lateral abdominal muscles in expiration. Electromyographic studies, however, show that this muscle has no effect on respiration but rather is concerned only with flexion of the trunk.[6]

It appears that thoracic excursion is accomplished by increased activity of the

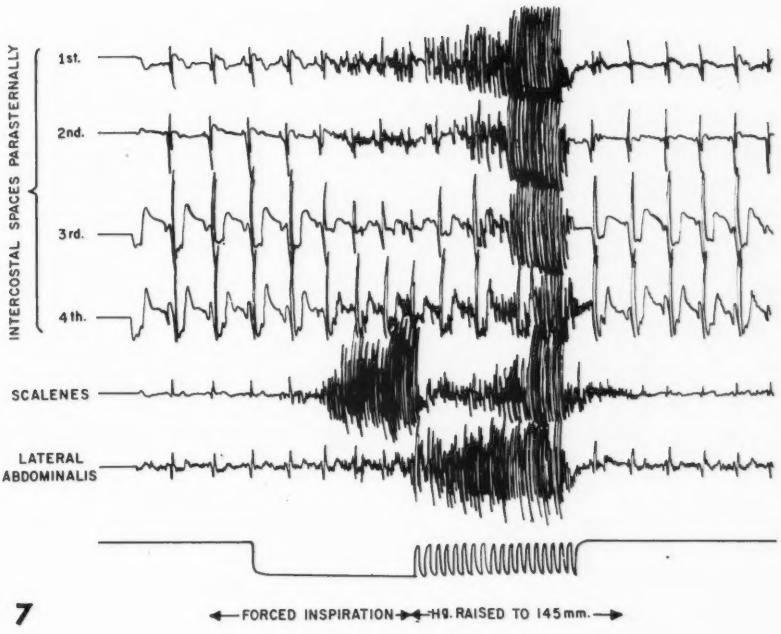


Figure 7

scalenes which raise the first ribs. Because the cage is so precisely balanced, the remaining ribs follow. Due to their axes of rotation, shape, differences in length and downward and forward position, their elevation produces an increase in the anterio-posterior as well as the transverse diameters of the chest. Since the individual intercostal muscles do not contract in quiet breathing, the ribs must be raised by their connections to the parietal pleura and its associated endothoracic fascia. As the first rib is elevated by the scalenes, the other ribs follow. It has been suggested that the scalenes only fix the first rib; but if this were true, then how could one explain the elevation of the ribs in eupnea where action potentials from the intercostal muscles are not recordable? Cessation of scalene activity permits the ribs to descend, and the cage assumes its resting position. In forced inspiration the strong contractions of the scalenes pull hard on the first rib, thus rapidly elevating the other ribs. Because the lower ribs are attached to the abdominal muscles, such a rapid elevation of the first rib would tend to widen the intercostal spaces and fan-out the ribs like the bellows of an accordion. Contraction of the intercostal muscles prevent the ribs from spreading apart and assist in preventing retraction of the intercostal spaces that might accompany the rapid decrease in intrathoracic pressure. In forced expiration and in blowing into a mercury manometer (Fig. 7), the lateral abdominal muscles pull down on the rib cage and the first rib is depressed. The intercostal muscles contract, thus opposing any tendency of bulging of the intercostal spaces due to the elevated intrathoracic pressure, and prevent the ribs from separating. The scalene muscles resist this sudden change, and their electromyographic tracings demonstrate their activity (Fig. 1).

Some readers may wonder why structures such as intercostal muscles exist. Would not a strong elastic or collagenous membrane between the ribs suffice to

keep them from spreading apart and bulging or retracting during forced respiratory movements? The answer is probably "yes." Such a membrane could serve adequately for breathing, but it would hinder body movement. For example, when a person leans to one side, the intercostal spaces narrow on the ipsilateral side and spread on the contralateral side. A membrane would hinder such a movement. Heavy collagenous attachments would assist the abdominal musculature when a person sat up from a supine position but would hinder him when he attempted to bend backwards from a standing position. An elastic membrane would permit the back bend but could not assist in sitting up. But the intercostal muscles are capable of holding the ribs in proper approximation as well as stretching to permit various body movements.

---

1. Martin, H. N. and Hartwell, E. M., J. Physiol., 2:24, 1879.
2. Hoover, C. F., Arch. Int. Med., *12*:214, 1913.
3. Hoover, C. F., Arch. Int. Med., *20*:701, 1917.
4. Hoover, C. F., Arch. Int. Med., *30*:1, 1922.
5. Bronk, D. W. and Ferguson, L. K., Am. J. Physiol., *110*:700, 1935.
6. Jones, D. S., Beargie, R .J. and Pauly, J. E., Anat. Rec., *117*:17, 1953.
7. Jones, D. S. and Pauly, J. E., Anat. Rec., *in press.*
8. Campbell, E. J. M., J. Physiol., *129*:12, 1955.
9. Koepke, G. H., Murphy, A. J., Rae, J. W. and Dickenson, D. G., Arch. Phy. Med., 36: 217, 1955.
10. Pauly, J. E., Jones, D. S., Jarach, A. and Toman, J. E. P., Fed. Proc., *16*:99, 1957.
11. Campbell, E. J. M. and Green, J. H., J. Physiol., *127*:423, 1955.
12. Campbell, E. J. M., J. Anat., *89*:378, 1955.

THE MEDICAL HISTORY — A CRITIQUE

HARRY H. GARNER, M.D.,* and ABRAHAM J. SIMON, Ph.D.**

The material covered in this discussion is the outgrowth of some thinking and philosophizing on certain standard concepts of medical history taking which have to a large extent permeated the medical curriculum. They are usually expressed in the rather rigid, possibly poorly conceived attitudes, of the average medical student by the time he has become a senior.

One of these general attitudes is that good medical practice requires thoroughness, and the taking of a complete medical history covers **all** the questions necessary to establish presence or absence of a disease system. Such thoroughness and completeness is supposed to epitomize the exactness of the scientific method and make for good medicine. A by-product of this attitude is that the physician rather mechanically runs through a battery of questions without a great deal of understanding of the patient's answers, other than the significance which a yes or no may have for a diagnostic entity which is being pursued. To illustrate: Presenting complaints of cough, pain in the chest and weight loss lead the examiner to consider tuberculosis of the lungs as a possible causative agent. He therefore becomes interested in the health of the patient's siblings, and causes of death, if any. The patient replies that he had one brother and four sisters, all of whom are now dead. The physician pursues this information, requesting to know the date and cause of death of each sibling. Having elicited no data bearing positively on TB, he goes on to the next item without interest in how the patient feels about being left virtually alone with the loss of so many siblings. Nor does he express any words of sympathy or understanding. The next item happens to be "occupation." Such an experience gives a patient the feeling of being approached in a very mechanical, depersonalized fashion.

In the "chief complaint and present illness" section of medical history taking, we have often been impressed by the frequency with which the patient presents a new, significant fact only to find that the examiner is not interested in what is to him "divergent" information, but insists on getting back to previously discussed material before being willing to think further about the case. This tendency is to a large extent dependent on the idea of "following through" on each complaint to the point of complete investigation before going on to any new step. Sometimes it seems as if the examiner is even exasperated at the patient for introducing what he sees as "irrelevant" to the material being pursued. This failure to recognize the relevance of historical data often leads one to ignore very significant material. While listening to the taking of a history dealing with the collapse of a patient on the street and of her revival by a pulmotor squad, one could be struck by the remark that people were laughing at her as she returned to consciousness. The doctor ignored the statement in order to pursue his inquiry about precordial distress which preceded the spell. The clue of laughter however, was sufficient as the first item in a chain of investigation which ultimately led to a more accurate evaluation of the patient's difficulty as part of a paranoid psychosis. Further development of the history established a non cardiac basis for the so-called collapse.

A quote from Dr. Robert Wartenburg, in the Current Medical Digest discussing history taking by the neurologist, is worth mentioning:

"The art of history-taking requires many things: observation and careful recording, credulity and critical judgment, guidance and 'laisser aller,' inquisitiveness and tact—all that makes a good physician. But it has its reward. History taking with sympathy and interest will contribute toward the main goal: that the

* Professor and Chairman, Department of Psychiatry, The Chicago Medical School.

** Chief, Social Science Section, Department of Psychiatry, The Chicago Medical School.

patient leave the office feeling better than when he entered."

The chief complaint, and the "onset and course of the present illness" is best obtained as a free flowing interview with the provision of reasonable interference with and redirection of excessive circumstantiality. An occasional question to develop and round out historical data will help give an integrated history. There is no difficulty for the examiner with obviously relevant and properly placed material. But significant parts of a history may be incongruities and inconsistencies, material often considered irrelevant by routine examiners. Stewart Wolff writes:

"Unaccountable memory defects for past and present events, contradictory statements, mention of a person or subject out of direct line of the story, damning with faint praise, and blocking or suddenly changing the subject before the previous thought has been developed; these and other signs in the interview, including gestures, facial expressions, and tone of voice give important information to the attentive observer about what make a patient tick. They are among the important data elicited by the skillful physician in talking with his patient."

The family history can frequently become an account of illnesses and deaths of parents and siblings, of familial diseases and of marital status, as if recording for the purpose of collecting statistics. On the other hand, the dates of death of people significant to the patient may give one an opportunity to study the presenting illness as being precipitated by such events. A recent birth may create feelings of insecurity which are more significant for explaining the patient's symptoms than a relatively minor drop in the blood count. The family history needs to be evolved as information enabling us to judge the significance of the interplay of emotional forces and events in the family in order to weigh the importance of these forces in the precipitation or perpetuation of the patient's present illness.

The social history is sometimes dealt with as a means to elicit corroborative evidence for an established diagnostic conclusion rather than as an opportunity to understand the social setting and its influence on the total person. If malaria is suspected, then information that the person lived in the South may be highlighted in the history. Suspicion of a nutritional disease may lead to a search for improper dietary habits. A toxic rather than a schizoid reaction may be "verified" by details of the patient's occupation as a painter giving exact data on how and with what he mixes his paint. Important data on the patient's social and economic status, his daily functioning, his isolated and ineffectual manner, and an erratic work history may be refused as "irrelevant." In this way, the diagnostic possibility of a schizophrenic reaction which could as well explain the patient's disability is not clarified, but obscured because the data in the social history is not adequately obtained or evaluated.

The three important goals of a medical history are listed by Carter as: (1) Establishing the initial relationship with the patient, (2) Acquiring sufficient information to be able to diagnose and treat, and (3) Keeping the patient as comfortable as is consistent with adequate diagnosis and treatment. In taking the social history the goal of acquiring sufficient information to diagnose and treat is frequently overlooked.

The history of infectious diseases, diet, allergic and immunologic responses, and general health often includes statements about past illnesses without any real confirmation, or even the supporting evidence of descriptive detail. To quote as fact the patient's statement that he had encephalitis three years ago, or a coronary one year ago, without even a description of the illness is in many instances to accept as fact either a misunderstanding or an error. In psychosomatic disorders particularly, it is a constant experience to conclude that a physical illness which is claimed to have been experienced in the past is of doubtful likelihood judging from elaborations of the history or from cumulative hospital records. These often fail to give data supporting a claim that the patient actually suffered from the disease.

The development of the "complete systemic review" leads to many distortions which can be called to one's attention only when the myth that scientific accuracy requires this type of investigation can be exposed. A very impressive thoroughness was shown by an examiner in the admitting clinic about a painful shoulder complaint. He was eliciting from the patient a systematic review of symptoms for arthritis, e.g. "Is the joint swollen?" "Is it red?" "Is it hot?" etc. After having exhausted the system inquiry, he felt satisfied. The patient's replies had been "yes". The physician had gathered the impression that he was dealing with a typical arthritic involvement of the shoulder, a painful, swollen, red joint. Another examiner then turned to the patient and asked, "Is it cold and white?" He again answered "yes."

The investigation of organ systems by leading questions as to the presence of certain symptoms tends to distort through "symptom giving." The patient's need to comply, to be the good patient, to please the examiner frequently leads to the acceptance of some symptoms as a reaction to the suggestive nature with which the inquiry about the symptom is made. In an earlier paper on medical history taking by indirect questioning, the senior author has more thoroughly discussed this problem.

One of the more frequent defenses against and attacks on the possibility of a diagnosis suggesting a "functional" condition is contained in the attitude: "You can't rule it out," "You should have a complete diagnostic workup," or "Everything must be ruled out before you can say it's functional." These self same expressions of the need for completeness, for avoidance of the error of overlooking structural disease, we are able to recall as being prevalent ideals of examination of our student days. It is not our purpose to minimize the desirability of diminishing error in diagnosis, or of the importance of a detailed investigation of the patient's problem. However, there is grave question as to whether or not this so-called thoroughness need imply the utilization of laboratory and other diagnostic procedures to the point of absurdity without offering the patient the benefits of an adequate personal diagnostic interview and physical examination. We feel that the teaching which prompts the student's need to say "You can't rule out," needs revision. The point being made can best be emphasized by a clinical situation.

A patient presented herself because of precordial pain, dyspnea an exertion, headache and backache. She was seen with a student after he had done a complete physical examination. When asked for a diagnostic impression, he replied, "She is probably a cardiac case." An inquiry as to his findings was followed by an admission that there were no cardiac findings. When asked what he would do to further the patient's care, he spoke in favor of a "cardiac workup" and described the need for ECG, chest plate for heart, etc. as further desirable examination procedures. It was pointed out that after all, physical examination had not disclosed any significant findings. The question was raised as to why investigate the possible cardiac symptoms by further laboratory procedures. Turning to the patient, she was asked about the chief cause for her clinic visit. The reply was "my headache." It was further learned that the pain in the back had developed as the patient's first symptom in the presenting complaints. If one were to carry the concept of a "complete diagnostic workup" to its ultimate conclusion, in such situations, it would lead to a rather absurd relationship to the patient. Yet our medical teaching leads to the very common statement: "The patient is entitled to an ECG" or whatever other diagnostic procedure the student may feel the patient is "entitled to." The patient complaining of severe pain in the back radiating into the legs with increase on coughing, etc., is often "entitled to" an X-ray of the back, but one may find that testing patellar and achilles reflexes in the lower extremities may be neglected unless the patient is being examined in neurology. It has been our impression that all too often, the so-called "complete diagnostic investigation to which the patient is entitled" is all too often limited to that group of symptoms which enable

the use of diagnostic procedures with which the examiner is most familiar, or can obtain with a minimum of effort.

It might seem that this discussion is primarily destructive. This is not our intent. But when we deal with a well established set of rules or concepts, it does seem best that weaknesses be pointed out before undertaking positive suggestions for change in the system. As the first of such suggestions, in the taking of presenting complaints, we feel it may be wiser for the examiner to allow the patient to digress freely for a reasonable period, should he tend to do so, and pursue material as the patient leads with it. If time interferes, or the material's relevance is not perceived, (material is never irrelevant, it is the examiner's inability to perceive and appreciate relevance that leads to the claim that the material is irrelevant) one may then redirect the patient to the presenting complaints.

The present illness, its onset and course history, is so frequently done in what can be called a "smash through center." The examiner catches the ball, fixes his eye on center, hopes there is an opening, and goes through if there is. It is our feeling that more flexibility than that is needed in medical history taking. It makes for better and more interesting medical work and improves patient-physician relationships. To illustrate: A patient notices a sudden sharp pain radiating down the right leg. The leg then becomes numb and walking progressively more difficult until she finds herself unable to move the right leg. An onset and course history elicited with greater flexibility from this same patient might also have read "Two weeks ago on Sunday, while on the way to church, the patient developed a pain radiating down her right leg. She was in a sad frame of mind at the time, having visited the graves of her parents the day before." Utilizing such information it becomes possible in this patient to uncover a emotionally traumatic situation involving guilt feeling over an intimate relationship with a friend who means a great deal to her. Her strict Lutheran up-bringing makes an association of the onset of her visiting her parent's grave, and going to church quite significant.

An onset and course history should not in our opinion, be symbolized by direct invasion of the patient as by a frontal assault. It can better be symbolized by a series of spirals in which the center of each spiral is a symptom being investigated. The symptom is clothed by the situation, events, places, persons, and emotional stresses and deprivations. One can then truly see these experiences as vestments of the symptom.

Some remarks pertaining to the improvement of the family, social, and past personal history have already been made. Failure to do an effective job within this area of inquiry is usually related to the examiner's need to pursue a possible organic diagnostic impression over against trying to understand the person in a holistic way.

The investigation of the patient in the systematic review of symptoms can much better be carried out through indirect questioning. Direct questioning, usually in the form of leading questions, successfully plant many seeds in the minds of even not particularly anxious patients through the power of suggestion. The greatest source of suggestive "symptom giving" is that part of the history which is generally referred to as the "inventory of symptoms." It is here that the physician, as traditionally trained, is likely to verbalize a list of complaints in a manner so beguiling as to offer a choice of symptoms previously not available to the patient. The number of such suggestive symptoms are too many to mention. Unfortunately the patient is rarely "offered" these only once. As a patient is seen by a series of physicians, so may the list be used on successive occasions. Hospitalization introduces him to another series of question askers. If they are leading questions, a whole symptom complex can become thoroughly fixed in his mind. A clearer concept of what is being stressed can be obtained by noting the manner in which an organ system examination is frequently made, and how a similar history can be elicited without any leading question activity suggesting a symptom.

A patient may be questioned for possible eye injury associated with blepharospasm by being confronted with such questions as: "Did something happen to your eyes?" "Can you open your eyes?" "Can you see?" "Does it hurt?" All of such questions suggest that the patient actually sustained an injury, that he may be unable to open his eyelids, and that he cannot see. They are reinforcing questions and suggestions which cumulatively tend to strengthen the idea that a serious disability exists. A preferable approach would reassure and suggest the opposite. If a real disability does not exist, indirect questioning can help convert the patient from one with a "disability" requiring hospitalization to one who can be immediately "cured." The following technique has been found successful. After an appraisal of the situation, the patient is told in a positive and reassuring manner: "Open your eyes." If there is hesitation, or delay he may be positively urged: "Make an effort to do so." An examination is then made of the eyeball to assure the examiner that no injury exists. The patient may be asked: "Tell me what happened." These questions to elicit further information about the patient's ocular symptoms may then be used: "What did you notice? "How were you affected?" "Did you notice any other symptoms?" "Is there anything else you can tell me?" "Is there anything about this you want to ask me?" etc. The material will be revealed freely without a single suggestive idea.

Another example of history-taking by the indirect method may more clearly demonstrate the more favorable potentialities of indirect versus direct questioning. A typical example of a history of being taken by direct questions, after the "initial complaint and history of the present illness" has been elicited, might proceed as follows: "Do you have stomach pain?" "How long have you had the pain?" "Do you vomit?" "Did you ever vomit before?" "Did you ever notice blood in your stools?" It is not uncommon to hear a series of such questions given to a patient complaining of epigastric pain or discomfort. We have found that just as good a picture can be obtained through indirect questioning with questions as: "Describe your discomfort." "Can you locate it for me?" "When did you first notice it?" "Where else did you notice it?" "Have you noticed anything else about your condition?" "What did you notice about your condition?" "What about your eating and appetite?" If the patient indicates that he has vomited: "What did you notice about your vomiting?" "What was in the stuff you vomited?" "Have you noticed anything different about your bowel movements or stool?" "Did you notice anything in your stools?" We have found that a perfectly satisfactory medical history can be obtained by using such indirect questions. The possibility of improving, and increasing available information through further indirect questioning constantly exists. The end result is a very adequate history without "giving" the patient a choice of new symptoms. The same method may be applied with equal success to any organ system.

The present tendency in medical "history taking" is based on the concept of a systematic investigation of the patient directed allegedly to obtaining a maximum degree of scientifically accurate information about a patient, and applying this information to the problem of a diagnostic evaluation. The ultimate goal of this procedure is that prognostic and therapeutic benefit may accrue to the patient from this investigation. It is felt that the application of some of the principles mentioned in this paper might lead to as adequate an approximation of the scientific wish fulfilling expectations of the examiner. But a more effective understanding of the patient as a whole person, and a continuously learning and growing experience for the examiner will be another end result.

BIBLIOGRAPHY

1. Carter, George: History Taking and Interviewing Technique, Journal of Medical Education, Vols. No. 5, 6, pp. 315-326, June 1955.
2. Garner, H. H.: Obtaining Medical Histories by Indirect Questioning, Quarterly of The Chicago Medical School, Vol. 9, No. 4, pp. 19-22, July 1942.
3. Preparation of Case Reports and Progress Notes. Dept. of Medicine, University of Illinois College of Medicine, September 1951.
4. Wolff, Steward: Talking with the Patient (considered for publication), Paul B. Hoeber, N.Y.

BOOKS RECEIVED

The following books have been received by this Quarterly. Their receipt is hereby acknowledged and this listing must be regarded as sufficient return for the courtesy of the sender. Those which appear to be of particular interest will be reviewed here as space permits. Additional information regarding all books listed will gladly be furnished upon request.

* * * * *

The Principles and Methods of Physical Diagnosis by Simon S. Leopold, M.D., Professor of Clinical Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania: Chief of the Thoracic Clinic, Hospital of the University of Pennsylvania with a Chapter on *Sounds from the Thorax:* Acoustic Principles by Reid S. Warren, Jr., Sc.D. in E.E., Professor of Electrical Engineering, the Moore School of Electrical Engineering, University of Pennsylvania. Second edition. Cloth, 537 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1957.

* * * * *

The Treatment of Burns by Curtis P. Artz, M.D., F.A.C.S., Lt. Col., MC, USA (Ret.), formerly, Director, Surgical Research Unit, Brooke Army Medical Center, Fort Sam Huston, Texas; Presently: Associate Professor of Surgery, University of Mississippi Medical Center, Jackson, Mississippi and Eric Reiss, M.D., American Cancer Society Scholar and Instructor in Medicine, Washington University School of Medicine, St. Louis, Missouri. With 199 Illustrations on 105 Figures. Illustrations by Burr Bush. Cloth, 250 pp. Philadelphia: W. B. Saunders Company, 1957.

* * * * *

Therapeutic Exercise for Body Alignment and Function by Marian Williams, Ph.D., Assistant Professor of Physical Therapy, Department of Allied Medical Sciences, School of Medicine, Stanford University, and Catherine Worthingham, Ph.D., Director of Professional Education, The National Foundation for Infantile Paralysis, Inc. With Exercise Illustrations by Harold Black. Paper, 127 pp. Philadelphia: W. B. Saunders Co. 1957.

* * * * *

Signs and Symptoms: Applied Pathologic Physiology and Clinical Interpretation. Edited by Cyril Mitchell MacBryde, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician, the Barnes Hospital; Director, Metabolism and Endocrine Clinics, Washington University Clinics, St. Louis, Missouri. With 28 Contributors. Third Edition. Cloth, with 191 illustrations and 6 color plates. Philadelphia: J. B. Lippincott Company, 1957.

* * * * *

Textbook of Pathology, With Clinical Applications, by Stanley L. Robbins, M.D., Associate Professor of Pathology, Boston University School of Medicine; Associate Director of the Mallory Institute of Pathology, Boston, Massachusetts; Lecturer, Harvard Medical School and Tufts University School of Medicine. Illustrated. Cloth. 1351 pp. Philadelphia: W. B. Saunders Co., 1957.

* * * * *

A Textbook of Histology, by Alexander A. Maximow, Late Professor of Anatomy, University of Chicago and William Bloom, Professor of Anatomy, University of Chicago. Seventh Edition. Cloth, with 1082 Illustrations, 265 in color, on 631 figures. Philadelphia: W. B. Saunders Company, 1957.

BOOK REVIEWS

Principles of Urology, by Meredith F. Campbell, M.S., M.D., F.A.C.S. Cloth. 1st edition. 622 pages. Philadelphia: W. B. Saunders Company, 1957. $10.00.

This new book has a twofold purpose, that of the instruction of the student in the broad fundamentals of urology, and as a practical guide for the physician who is not a urologic specialist, as he encounters urologic problems.

A brief review of the more important aspects of urogenital tract anatomy and physiology are included as an introductory refresher. Urologic symptoms and their potential significance as indications for special urologic examination are discussed, while the pathogenesis, clinical aspects, diagnosis and treatment of the more common urologic diseases are adequately considered for the needs of active daily general practice either in the office or at the bedside. The reader is instructed in the requisites of physical and laboratory examination and diagnostic study up to the point of cystoscopic investigation and major urosurgical treatment. Minor office procedures such as meatotomy and the passage of catheters and sounds are illustrated.

A useful and stimulating inclusion in this book is a chapter of questions with page references to the answers.

L.W.D.

GIFFORD'S TEXTBOOK OF OPHTHALMOLOGY, by Francis H. Adler, M.D.; 6th Edition, 499 pages, illustrated with 277 figures and 26 color plates. Philadelphia: W. B. Saunders Co., 1957.

Gifford's classic, has continued as he has done in the past, to present a text which can be used as an up-to-date practical guide by medical student and general practitioner alike. It is a concise presentation of the most commonly occurring disease processes and injuries of the eye and adnexa.

The book is quickly read, clearly presented and in a very pallatable form. The line drawings, black and white and color photographs which illustrate the text highlight most of the salient features of the anatomy, pathology, examining technics and examples of testing results related to ophthalmology. In this new edition the author has enlarged the chapter on Occular Manifestations of General Diseases, especially the sections on viral and degenerative diseases. Other fine sections frequently overlooked in other books on the subject are on emergency waiting room and recovery ward procedures and there is an excellent chapter on orientation of surgical operations on the eye and adnexa.

This volume is heartily recommended as a reference work for the medical student, who can use it as a textbook to good advantage. Likewise, it will prove useful to any physician desiring a clear, concise exposition of ophthalmologic problems. It is probably too abbreviated a volume to be a great value to the practicing eye specialist, but surely this was not the author's purpose in writing it.

ABSTRACTS SECTION

FURTHER ELECTROMYOGRAPHIC STUDIES ON MUSCLES OF COSTAL RESPIRATION IN MAN —David S. Jones and John E. Pauly, Departments of Anatomy, The Stritch School of Medicine, Loyola University, The Chicago Medical School, Chicago Illinois—Anatomical Record—in press.

Electromyographic studies were made on the scalenes, intercostals and lateral abdominal muscles by means of two ink writing modified electroencephalographs. The scalenes and intercostals contract in hyperpnea during the inspiratory and beginning of the expiratory phase. The lateral abdominals produce action potentials at the end of inspiration and during expiration. The continuation of activity of the scalenes and intercostals from the inspiratory over into the expiratory phase is interpreted as indicating that some force is necessary to prevent sudden emptying of the lungs from the fully expanded state. The fact that intra-abdominal pressure increases toward the end of forced inspiration and that the rapidly elevated rib cage tends to stretch the lateral abdominal muscles, leads us to advance the argument that abdominal muscular contractions, at least during inspiration, are initiated by the muscle stretch reflex.

A maximum expiratory effort into the tube of a mercury manometer elicits action potentials from the scalenes as well as the lateral abdominal muscles and intercostals.

Contractions of the intercostal muscles occur during various movements of the trunk. It is obvious that the intercostals as well as the scalenes and lateral abdominals act in postural adjustments and perhaps are used in nonrespiratory activity more than in ordinary respiration.

* * * * *

FOA, P. P.: La Fisiopatologia del Diabete. Atti Soc. Lombarda Sci. Med.-Biol., 11:301, 1956.

A review on the physiopathology of diabetes, written in Italian. 228 references.

POLLI, JOHN F. and LUISADA, ALDO A. (*Chicago Medical School at Mount Sinai Hospital, Chicago, Ill.*): Effect of Splenectomy, Nephrectomy and Other Procedures on Epinephrine-induced Pulmonary Edema. Am. J. Physiol. 188(3): 599-603. 1957.

The effect of various operative procedures and tissue extracts on epinephrine-induced pulmonary edema (EPE) was studied in 338 rabbits. Anesthesia and laparotomy with manipulation of the viscera had a definite protective effect against EPE. Similar effects were obtained with the intraperitoneal injection of a foreign substance or pretreatment with ACTH or adrenal cortex steroids. This protection is believed to be the result of adrenal cortical activation by stress. Splenectomy had a protective effect against EPE which was greater than that of sham operations. The injection of splenic extract in splenectomized animals decreased survival time and increased the severity of the edema, whereas injection of hepatic extract had a less marked effect. Both unilateral and bilateral nephrectomy had a protective effect against EPE.

* * * * *

PAULY, JOHN E.: Glycogen Stores in Glucagon-Treated Rats. III. Effects of Adrenalectomy and Hypophysectomy. Proc. Soc. Exp. Biol. and Med. 94:417. 1957.

The effect of glucagon and epinephrine on liver and muscle glycogen of adrenalectomized and hypophysectomized rats with or without treatment with cortisone or insulin was studied.

The results are consistent with the hypothesis that glycogenolysis and hyperglycemia are the primary effects of glucagon and epinephrine and that the delayed increase in liver glycogen and occasionally of muscle glycogen, observed after injection of these hormones, is the result of a secondary secretion of insulin aided by the "permissive" action of the adrenal cortex.